Antipsychotics
Therapeutic Class Review (TCR)

August 27, 2015

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Other Indications	Schizophrenia	Psychotic Disorders	Bipolar Disorder (acute manic episodes)
First Generation Antipsychotics – Oral					
amitriptyline / perphenazine[1]	generic	Psychotic depression with symptoms of anxiety or agitation	--	--	--
chlorpromazine[2]	generic	Acute intermittent porphyria, hiccups, presurgical apprehension, N/V, adjunct in the treatment of tetanus	X	X	X
fluphenazine[3]	generic	--	--	X	--
haloperidol[4]	generic	Hyperactivity (children) with conduct disorder, Tourette's disorder (children and adults)	--	X	--
*molindone (Moban®)[5]	Endo*	--	X	--	--
perphenazine[6]	generic	N/V	X	X	--
pimozide (Orap®)[7]	Gate Pharmaceuticals	Tourette's disorder (second line)	--	--	--
thioridazine[8]	generic	--	X (second-line)	--	--
thiothixene (Navane®)[9]	generic	--	X	--	--
trifluoperazine[10]	generic	Non-psychotic anxiety (second line)	X Includes ages 6 to 17 years	--	--

N/V = nausea/vomiting

* Endo has discontinued production of Moban. Supplies were expected to be depleted in June 2010.

FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Psychotic Disorders	Bipolar Disorder (acute manic episodes)
First Generation Antipsychotics – Injectable					
fluphenazine decanoate[11]	generic	--	X	--	--
haloperidol decanoate (Haldol® Decanoate)[12]	generic	--	X	--	--
First Generation Antipsychotics – Inhaled					
loxapine inhalation powder (Adasuve®)[13]	Teva Select Brands	--	X	--	X (acute agitation)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral							
aripiprazole (Abilify®)[14]	generic, Otsuka	Adjunctive treatment of depression in adults; Treatment of irritability associated with autistic disorder (Includes ages 6-17 years); Treatment of Tourette's disorder	X Adults and adolescents (ages 13-17)	X Adults and pediatrics (ages 10-17) monotherapy and in combination with lithium or valproate	--	X Monotherapy and in combination with lithium or valproate (ages 10-17 years)	X Adults monotherapy and in combination with lithium or valproate
brexpiprazole (Rexulti®)[15]		Adjunctive treatment of major depressive disorder (in adults)	X (adults)	--	--	--	--
asenapine (Saphris®)[16]	Schering	--	X (adults)	X Adults and pediatrics (ages 10-17) monotherapy and in combination with lithium or valproate in adults	--	X Adults and pediatrics (ages 10-17) monotherapy and in combination with lithium or valproate in adults	--

FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral							
clozapine (Clozaril®)[17]	generic	--	X Refractory schizophrenia or to reduce suicidal behavior in schizophrenia or schizoaffective disorder	--	--	--	--
clozapine (Fazaclo®)[18]	Jazz Pharmaceuticals	--					--
clozapine (Versacloz™)[19]	Jazz Pharmaceuticals	--		--	--	--	--
iloperidone (Fanapt™)[20]	Novartis	--	X	--	--	--	--
lurasidone (Latuda®)[21]	Sunovion	--	X	--	X (monotherapy and in combination with lithium or valproate in adults)	--	--
olanzapine (Zyprexa®)[22]	generic	Acute treatment of treatment-resistant depression (in combination with fluoxetine); Pediatric treatment of bipolar I disorder after thorough evaluation and risk assessment	X Adults; Adolescents (ages 13-17) second-line; Pediatric treatment after thorough evaluation and risk assessment	X Adults monotherapy and in combination with lithium or valproate; Adolescents (ages 13-17) second line	X (in combination with fluoxetine)	X Acute adult monotherapy and in combination with lithium or valproate; Adolescents (ages 13-17) second line	X Treatment of bipolar I disorder
olanzapine/ fluoxetine (Symbyax®)[23]	generic	Treatment-resistant depression	--	--	X	--	--

FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral *(continued)*							
paliperidone ER (Invega®)[24]	Janssen Pharmaceuticals	Adults treatment of schizoaffective disorder (monotherapy or adjunct with mood stabilizers and/or antidepressants)	X Adults; Adolescents (ages 12-17)	--	--	--	--
quetiapine (Seroquel®)[25]	generic	Adults-Depressive disorder associated with bipolar I or II disorder	X Adults; Adolescents (ages 13-17)	X Adults and adolescents (ages 10-17) monotherapy and in combination with lithium or divalproex	X	--	X Adults in combination with lithium or divalproex
quetiapine XR (Seroquel XR®)[26]	AstraZeneca	Adjunctive treatment of major depressive disorder in adults; Maintenance treatment of bipolar disorder in adults in combination with lithium or divalproex	X in adults and in adolescents (13-17 years of age)	X monotherapy and in combination with lithium or divalproex in adults; in children and adolescents (10-17 years of age)	X Acute episodes in adults	X monotherapy and in combination with lithium or divalproex in adults	X In combination with lithium or divalproex in adults

FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral *(continued)*							
risperidone (Risperdal®)[27]	generic	Treatment of irritability associated with autistic disorder (ages 5-16 years)	X Adults; Adolescents (ages 13-17)	X Adults monotherapy and in combination with lithium or valproate; Children (ages 10 to 17) monotherapy	--	X Adults monotherapy and in combination with lithium or valproate; Children (ages 10-17) monotherapy	--
ziprasidone (Geodon®)[28]	generic	Maintenance treatment of bipolar disorder in adults in combination with lithium or divalproex	X	X	--	X	X Adults in combination with lithium or divalproex

FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Psychotic Disorders	Bipolar Disorder
Second Generation Antipsychotics – Injectable					
aripiprazole (Abilify® Injection)[29]	Otsuka	--	X (acute agitation)	--	X Agitation associated with bipolar disorder
aripiprazole ER (Abilify Maintena™)[30]	Otsuka	--	X	--	--
olanzapine (Zyprexa®)[31]	Eli Lilly	--	X (acute agitation)	--	X Acute treatment of agitation associated with mania
olanzapine (Zyprexa® Relprevv)[32]	Eli Lilly	--	X (maintenance treatment)	--	--
paliperidone palmitate (Invega Sustenna®)[33]	OMJPI	Schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants	X (maintenance treatment)	--	--
paliperidone palmitate (Invega Trinza™)[34]	OMJPI	--	X (treatment in patients after they have been adequately treated with Invega Sustenna for at least 4 months)	--	--
risperidone (Risperdal® Consta®)[35]	OMJPI	--	X	--	X (monotherapy or in combination with lithium or valproate) Maintenance treatment
ziprasidone (Geodon®)[36]	Pfizer	--	X (acute agitation)	--	--

OVERVIEW

Schizophrenia

The most common psychotic illness is schizophrenia, which affects 1% of the population. Between 25 and 50% of schizophrenic patients attempt suicide, and 10% of patients succeed in their attempt.[37] The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for the diagnosis of schizophrenia includes first ruling out other disorders, and then assessing whether the disturbance has lasted for at least 6 months and includes at least 1 month of 2 or more characteristic symptoms.[38] These symptoms include delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms, and at least 1 of these should be delusions, hallucinations, or disorganized speech. Symptoms of schizophrenia can be subcategorized as positive, negative, cognitive, aggressive/hostile, and depressive/anxious.

Since schizophrenia is a chronic illness that afflicts all aspects of life, the goals of treatment, according to the 2004 American Psychiatric Association (APA) guidelines, are to stabilize the patient and reduce or eliminate the symptoms, improve quality of life and adaptive functioning, and reduce the likelihood of relapse.[39] Antipsychotics are the standard drugs used in patients with schizophrenia to achieve these goals. This guideline recommends a second generation antipsychotic (SGA) as first-line therapy due to the decreased risk of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), with first generation antipsychotics (FGA) suggested as appropriate first-line options for some patients. The 2009 Guideline Watch from the APA modifies this recommendation to state that FGAs may be equally effective as second generation agents. This statement is based on studies that have been published since 2002.[40]

Bipolar Disorder

Bipolar disorder is characterized by episodes of mania, depression, or a mixed state. Criterion used to diagnose bipolar I disorder is the presence of a manic episode (persistent elevated, expansive, or irritable mood for at least 1 week with increased energy/activity) or a mixed features specifier (rapidly alternating polarity of mood, sadness, irritability, and mania for at least 1 week), and 3 or more other characteristic symptoms are present.[41,42] These symptoms include inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressured speech, flight of ideas or feelings of racing thoughts, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in risky, pleasurable activities. The hallmark of a true manic episode results in symptoms severe enough to cause significant impairment in functioning, requires hospitalization to prevent harm to self or others, or includes the presence of psychotic features.

Criterion used to diagnose a bipolar II disorder includes one or more depressive episodes nearly every day during the same 2-week period with at least 1 hypomanic episode lasting at least 4 days. The depressive episodes are marked by the appearance of 5 or more depressed symptoms, which include a depressed mood most of the day every day, diminished interest in activities and hobbies, significant weight change, insomnia or hypersomnia, psychomotor agitation or retardation nearly every day, fatigue, feeling of guilt or worthlessness, indecisiveness or inability to concentrate, and recurrent thoughts of death or suicide. Hypomanic episodes are defined as a persistently elevated, expansive, or irritable mood with increased energy/activity and 3 or more other symptoms. These symptoms include inflated self-esteem, decreased need for sleep, pressured speech, distractibility, increase in goal-directed behavior, and excessive involvement with risky activities. The diagnosis of hypomania is very

similar to mania, but the episodes do not result in significant impairment of functioning; they do not necessitate hospitalization and no psychotic symptoms are present.

There is no cure for bipolar disorder, but the appropriate pharmacological treatment can decrease morbidity and mortality associated with the disorder. According to the 2002 APA guidelines, first-line pharmacological treatment for more severe manic or mixed episodes requires the initiation of lithium or valproate plus an antipsychotic agent. SGAs are preferred over the FGAs due to their more tolerable adverse effect profile.[43] As noted in the 2009 update to the APA guidelines for schizophrenia, however, there have been many comparisons between first and second generation antipsychotics since 2002. For a bipolar manic episode with less severity, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. Use of standard antidepressants as monotherapy can precipitate a manic episode in bipolar patients. Use of antidepressants in bipolar patients, misdiagnosed as having non-bipolar depression, can precipitate the first manic episode. During maintenance treatment, recommendations suggest to first optimize the medication dose in patients with bipolar disorder, especially in patients experiencing a breakthrough manic episode, and then consider adding another first-line agent if dose optimization of the initial agent does not lead to a satisfactory response. Another option is to change antipsychotic agents and monitor the patient for response.

The first-line treatment, according to the 2002 APA guidelines and for a bipolar depressive disorder, includes treatment initiation with lithium or lamotrigine; antidepressant monotherapy is not recommended. An alternative treatment option for more severe depressive episodes is the initiation of lithium with an antidepressant. Finally, if an acute depressive episode does not respond to the optimal dose of first-line medication treatment, then the addition of lamotrigine, bupropion, or paroxetine is recommended. Patients with bipolar depression experiencing psychotic features usually require adjunctive treatment with an antipsychotic.

Following remission of an acute episode, patients may remain at particularly high risk of relapse for a period of up to 6 months. This phase of treatment is considered in the APA guideline as part of the maintenance phase. The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine. If one of these medications was used to achieve remission from the most recent depressive or manic episode, it generally should be continued. For patients treated with an antipsychotic medication during the preceding acute episode, the need for ongoing antipsychotic treatment should be reassessed. Varying levels of evidence exist for maintenance treatment of bipolar disorder. Approvals have been given to aripiprazole and risperidone (long-acting injection) for monotherapy treatment of bipolar maintenance. Additionally, approvals have been given to quetiapine, quetiapine XR, and ziprasidone when used in combination with lithium of valproate in maintenance therapy.

Depression

According to the APA, for patients who exhibit psychotic symptoms during an episode of major depressive disorder (MDD), treatment should include a combination of antipsychotic and antidepressant medications or electroconvulsive therapy (ECT).[44] SGA medications may increase the rates of response or remission of depressive symptoms in patients who typically have not responded to more than 2 antidepressants, even when psychotic symptoms are not present. Generally, in clinical practice, lower doses are used for antidepressant augmentation than for treatment of psychosis.

PHARMACOLOGY[45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77]

First generation antipsychotics exert their therapeutic effect primarily by blockade of the dopamine-2 (D_2) receptors in the mesolimbic dopamine pathway. The blockade reduces the hyperactivity in this pathway and, thereby, potentially reduces the positive symptoms associated with psychosis. These agents also block the D_2 receptors in other pathways of the brain, resulting in their potential induction of negative and cognitive symptoms, extrapyramidal symptoms (EPS), tardive dyskinesia (TD), and hyperprolactinemia.

Antipsychotics block other receptors in varying degrees, largely resulting in additional adverse effects. Blockade of the muscarinic-cholinergic receptors can cause adrenergic blockade, which can result in orthostatic hypotension and drowsiness; dry mouth and blurred vision can be associated with the anticholinergic effects. Antagonism of the alpha-1 and histamine receptors has been proposed as one of the mechanisms leading to weight gain and drowsiness with antipsychotics.

The second generation antipsychotics (SGAs) are serotonin-dopamine antagonists. They differ from first generation antipsychotics (FGAs) in their "limbic-specific" dopamine type 2 (D_2)-receptor binding and high ratio of serotonin type 2 (5-HT_2) receptor binding to D_2 binding. These agents also have a lower affinity for D_2 receptors and, therefore, have faster dissociation with the receptor. Clinical properties that differentiate them from the FGAs are their reduced incidence of EPS and a decreased impact on prolactin levels.

Brexpiprazole (Rexulti) is pharmacologically similar to aripiprazole (Abilify, Abilify Maintena); both are partial dopamine and 5-HT_{1A} agonists rather than full dopamine agonists.

However, the higher affinity for the affected receptors has not been without serious adverse events. As indicated in the next table, effects of the SGAs on various receptors differ among agents. It is likely that the differences among these agents results from their varying effect on receptors other than their antagonism of 5-HT_{2A} and D_2 receptors. These ancillary pharmacologic properties include binding to D_1, D_3, and D_4 receptors; to 5-HT_{1A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, and 5-HT_7 receptors; to α_1-adrenergic, α_2-adrenergic, histamine H_1, and muscarinic cholinergic receptors.

Receptor Effects

Drug	Receptor Antagonist	Receptor Agonist	Receptors Bound with High Affinity	Receptors Bound with Moderate Affinity	Receptors Bound with Weak Affinity
First Generation Antipsychotics					
chlorpromazine	Adrenergic, peripheral anticholinergic, histaminergic, serotonergic	--	Adrenergic	--	Peripheral anticholinergic, histaminergic, serotonergic
fluphenazine	D_2, H_1, α, 5-HT_2	--	Not specified		
haloperidol	D_2, H_1, α, 5-HT_2	--	Not specified		
loxapine inhalation powder (Adasuve)	D_2, H_1, α_2, 5-HT_2, M_1	--	$D_{1\text{-}4}$, 5-HT_2	--	--
molindone (Moban)	D_2, α, 5-HT_2	--	--	--	D_2, α, 5-HT_2
perphenazine	D_2, H_1, α	--	Not specified		
pimozide (Orap)	D_2, others unspecified	--	Not specified		
thioridazine	D_2, H_1, α, 5-HT_2, M_1	--	Not specified		
thiothixene (Navane)	D_2, H_1, α	--	D_2	--	H_1, α
trifluoperazine	D_2, H_1, α, 5-HT_2, M_1	--	Not specified		

D = dopamine | α = alpha | β = beta

5-HT = serotonin | M = muscarine | H = histamine

GABA = gamma aminobutyric acid | BZD = benzodiazepine | NE = norepinephrine

Drug	Receptor Antagonist	Receptor Agonist	Receptors Bound with High Affinity	Receptors Bound with Moderate Affinity	Receptors Bound with Weak Affinity
Second Generation Antipsychotics					
aripiprazole (Abilify)	5-HT_{2A}, 5-HT_{2C}, 5-HT_7, α_1, H1, 5-HT reuptake site	Partial agonist: D_2, 5-HT_{1A}	D_2, D_3, 5-HT_{1A}, 5-HT_{2A}	D_4, 5-HT_{2C}, 5-HT_7, α_1, H_1, 5-HT reuptake site	--
asenapine (Saphris)	D_2, 5-HT_{2A}	--	$D_{1\text{-}4}$, 5-$HT_{1A\text{-}B}$, 5-$HT_{2A\text{-}C}$, 5-$HT_{5\text{-}7}$, $\alpha_{1\text{-}2}$, H_1	H_2	--
brexpiprazole (Rexulti)	5-HT_{2A}, 5-HT_{2B}, 5-HT_7, α_{1A}, α_{1B}, α_{1D}, α_{2C}	Partial agonist: D_2, D_3, 5-HT_{1A}	Not specified		
clozapine (Clozaril, Fazaclo, Versacloz)	$D_{1\text{-}5}$, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, M_1, M_2, M_3, M_5, α_1, α_2, H_1	M_4	D_4	--	--

Receptor Effects (continued)

Drug	Receptor Antagonist	Receptor Agonist	Receptors Bound with High Affinity	Receptors Bound with Moderate Affinity	Receptors Bound with Weak Affinity
Second Generation Antipsychotics *(continued)*					
iloperidone (Fanapt)	D_2, 5-HT_2	--	D_{2-3}, 5-HT_{2A}	D_4, 5-HT_{6-7}, $NE_{\alpha 1}$	D_1, 5-HT_{1A}, H_1
lurasidone (Latuda)	D_2, 5-HT_{2A}, 5-HT_7, α_{2A}	5-HT_{1A}	D_2, 5-HT_{2A}, 5-HT_7	α_{2C}	--
olanzapine (Zyprexa, Zyprexa Relprevv)	D_{1-4}, 5-HT_{2A}, 5-HT_{2C}, α_1, H_1, M_{1-5}	--	D_{1-4}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, α_1, H_1	5-HT_3, M_{1-5}	$GABA_A$, BZD, β
olanzapine/ fluoxetine (Symbyax)	D_{1-4}, 5-HT_{2A}, 5-HT_{2C}, α_1, H_1, M_{1-5}	--	D_{1-4}, 5-HT_{2A}, 5-HT_{2C}, α_1, H_1, M_{1-5}	--	$GABA_A$, BZD, β
paliperidone ER (Invega)	D_{1-4}, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, α_1, α_2, H_1	--	D_2, 5-HT_2, α_1, α_2, H_1	5-HT_{1C}, 5HT_{1D}, 5-HT_{1A}	D_1, haloperidol-sensitive sigma site
quetiapine (Seroquel)	D_1, D_2, 5-HT_{1A}, 5-HT_2, α_1, α_2, H_1	--	NE transporter with norquetiapine	--	--
quetiapine (Seroquel XR)	D_1, D_2, 5-HT_{1A}, 5-HT_{2A}, α_1b, α_2, H_1	--	NE transporter with norquetiapine	--	--
risperidone (Risperdal)	D_{1-2}, 5-HT_{1A}, 5-HT_{2A}, α_1, α_2, H_1	--	D_2, 5-HT_2, α_1, α_2, H_1	5-HT_{1C}, 5HT_{1D}, 5-HT_{1A}	D_1, haloperidol-sensitive sigma site
ziprasidone (Geodon)	D_2, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1B}, 5-HT_{1D}, α_1, H_1, synaptic 5-HT and NE reuptake	5-HT_{1A}	D_2, D_3, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1D}, α_1	H_1	--

D = dopamine | α = alpha | β = beta

5-HT = serotonin | M = muscarine | H = histamine

GABA = gamma aminobutyric acid | BZD = benzodiazepine | NE = norepinephrine

PHARMACOKINETICS[78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117]

Drug	Bioavailability (%)	Half-life (hr)	Active Metabolites	CYP450 Enzyme System
First Generation Antipsychotics – Oral				
amitriptyline	N/A	10-50	nortriptyline (half-life 20-100 hours)	Substrate: 3A4, 2C9, 2D6
chlorpromazine	19-51	23-37	7-hydroxychlorpromazine (half-life 10-40 hours)	--
fluphenazine	2.7 (oral); 3.4 (IM)	18 (oral)	--	--
haloperidol	60	24 (oral)	--	--
molindone (Moban)	N/A	12	--	--
perphenazine	N/A	9	--	Substrate: 2D6
pimozide (Orap)	40-50	55	--	Substrate: 3A4 and to a lesser extent 1A2 and 2D6
thioridazine	N/A	24	mesoridazine and sulphoridazine	--
thiothixene (Navane)	N/A	Biphasic 3.4 initial, 34 terminal	--	--
trifluoperazine	N/A	18	--	--
First Generation Antipsychotics – Injectable				
fluphenazine decanoate	N/A	N/A	--	--
haloperidol decanoate (Haldol Decanoate)	N/A	3 weeks	--	--
First Generation Antipsychotics – Inhaled				
loxapine inhalation powder (Adasuve)	N/A	7.61	multiple metabolites	Substrate: 1A2, 3A4, 2D6

IM = intramuscular; N/A = not available

Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-life (hr)	Active Metabolites	CYP450 Enzyme System
Second Generation Antipsychotics – Oral				
aripiprazole (Abilify)	87	75	dehydro-aripiprazole (half-life 94 hours)	Substrate: 2D6, 3A4
asenapine (Saphris)	35	24	--	Substrate: 1A2 (predominantly), 3A4, 2D6
brexpiprazole (Rexulti)	95	91	DM-3411 (half-life 86 hours; does not contribute to the therapeutic effects of brexpiprazole)	Substrate: 2D6, 3A4
clozapine (Clozaril, Fazaclo, Versacloz)	--	12	--	Substrate: 1A2, 2D6, 3A4
iloperidone (Fanapt)	well absorbed	18-33	P88 (half-life 26-37 hours)	Substrate: 2D6, 3A4
lurasidone (Latuda)	9-19	18	ID-14283, ID-14326	Substrate: 3A4
olanzapine (Zyprexa)	>57	21-54	--	Substrate: 1A2, 2D6
olanzapine/ fluoxetine (Symbyax)	--	21-54 / 4-6 days	norfluoxetine (half-life 16 days)	Substrate: 1A2, 2D6
paliperidone ER (Invega)	28	23	--	Substrate: 2D6, 3A4 (minor)
quetiapine (Seroquel)	100	6	N-desalkyl quetiapine (norquetiapine)	Substrate: 3A4
quetiapine XR (Seroquel XR)	--	7	N-desalkyl quetiapine (norquetiapine)	Substrate: 3A4
risperidone (Risperdal)	70	3 (extensive metabolizers); 20 (poor metabolizers)	9-hydroxyrisperidone (paliperidone) (21 hours is extensive metabolizers and 30 hours in poor metabolizers)	Substrate: 2D6
ziprasidone (Geodon)	60	7	--	Substrate: 3A4, 1A2 (minor)

Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-life (hr)	Active Metabolites	CYP450 Enzyme System
Second Generation Antipsychotics – Injectable				
aripiprazole (Abilify)	100	N/A	dehydro-aripiprazole	Substrate: 2D6, 3A4
aripiprazole ER (Abilify Maintena)	N/A	29.9-46.5 days	dehydro-aripiprazole	Substrate: 2D6, 3A4
olanzapine (Zyprexa)	N/A	21-54	--	Substrate: 1A2, 2D6
olanzapine (Zyprexa Relprevv)	N/A	30 days	--	Substrate: 1A2, 2D6
paliperidone palmitate (Invega Sustenna)	N/A	25-49 days	--	Substrate: 2D6, 3A4 (minor)
paliperidone palmitate (Invega Trinza)	N/A	84—95 days (deltoid injections); 118—139 days (gluteal injections)	--	Substrate: 2D6, 3A4 (minor)
risperidone (Risperdal Consta)	N/A	72-144	9-hydroxyrisperidone (paliperidone)	Substrate: 2D6
ziprasidone (Geodon)	100	2-5	--	Substrate: 3A4, 1A2 (minor)

CONTRAINDICATIONS/WARNINGS[118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140]

Contraindications

Concomitant use of clozapine (Clozaril, Fazaclo, Versacloz) with other agents that have the potential to cause agranulocytosis or otherwise suppress bone marrow function is contraindicated. Clozapine is contraindicated in patients with myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, history of clozapine-induced agranulocytosis or severe granulocytopenia, and severe CNS depression or comatose states.

Similarly, chlorpromazine, fluphenazine, haloperidol, molindone (Moban), perphenazine, pimozide (Orap), thioridazine, and trifluoperazine are contraindicated in patients who are comatose or have greatly depressed states because of CNS depressants or other causes. Thioridazine is also contraindicated for co-administration with other drugs that prolong the QT interval and in patients with congenital long QT syndrome or history of cardiac arrhythmias.

Fluphenazine, perphenazine, and trifluoperazine are contraindicated in patients with blood dyscrasias, bone marrow depression, or pre-existing liver damage. Fluphenazine is contraindicated in the presence of suspected or established subcortical brain damage. Thioridazine is contraindicated in patients with hypertensive or hypotensive heart disease of extreme degree.

Haloperidol is contraindicated in patients with Parkinson's disease. Thiothixene (Navane) is contraindicated in the presence of circulatory collapse or blood dyscrasias.

Pimozide is contraindicated in the treatment of simple tics or tics other than those associated with Tourette's Disorder. Pimozide should not be taken by patients who are taking other drugs that may cause motor or phonic tics.

The QT interval is prolonged by pimozide, so patients with cardiac conduction abnormalities should not take this drug. For similar reasons, use of pimozide concurrently with CYP3A4 inhibitors (such as macrolide antibiotics, azole antifungals, or protease inhibitors) is contraindicated.

Loxapine inhalation powder (Adasuve) is contraindicated in patients with a current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm or current use of medications to treat airways disease (asthma or COPD). Inhaled loxapine should not be taken by patients with acute respiratory symptoms or signs, such as wheezing, or by patients with a history of bronchospasm following inhaled loxapine treatment.

Co-administration with strong CYP3A4 inhibitors or inducers is contraindicated with the use of lurasidone (Latuda).

Boxed Warnings

All antipsychotics have a boxed warning regarding an increased incidence of mortality when these agents are used in elderly patients with dementia-related psychosis.[141] A review of 17 placebo-controlled trials revealed a rate of death in the elderly patients who received second generation antipsychotics of approximately 4.5% as compared to a rate of approximately 2.6% in placebo-treated patients. The causes of death were varied.

Quetiapine (Seroquel, Seroquel XR), olanzapine/fluoxetine (Symbyax), and aripiprazole (Abilify) have the same boxed warning as the antidepressants in regards to an increased risk of suicidality in children, adolescents, and young adults; therefore, close monitoring for signs and symptoms of suicidality in this patient population should occur.

Clozapine (Clozaril, Fazaclo, Versacloz) has several additional boxed warnings:

- Due to a significant risk of agranulocytosis (cumulative incidence at 1 year of 1.3%), clozapine should be reserved for use in severely ill patients with schizophrenia, who fail to show an acceptable response to adequate courses of standard antipsychotic treatment, or for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder, who are judged to be at risk of re-experiencing suicidal behavior. Patients must have a baseline white blood cell (WBC) count and absolute neutrophil count (ANC) before initiation of treatment, regularly during treatment, and for at least four weeks after discontinuation of treatment.
- Seizures are associated with the use of clozapine (cumulative incidence at 1 year of 5%); this is a dose-related effect. Caution must be used when administering clozapine to patients with a history of seizures or predisposition to seizures. Patients must also be warned to avoid engaging in activities where a loss of consciousness may cause harm to themselves or others.
- Myocarditis occurs with clozapine at a rate of 5 cases per 100,000 patient years; over half of these cases were fatal.

- Orthostatic hypotension with rare collapse (1 case per 3,000 patients) and respiratory and/or cardiac arrest occur at a higher rate in patients receiving clozapine, especially during dose escalation in the initial titration phase. The incidence also appears higher in patients receiving other psychotropic drugs.

Thioridazine has a boxed warning regarding its tendency to prolong the QTc interval in a dose-related manner.

Olanzapine (Zyprexa Relprevv) has a boxed warning stating that patients are at risk for Post-injection Delirium Sedation Syndrome (PDSS). This syndrome may result in severe sedation, including coma, and/or delirium after each injection. Patients should be observed for at least 3 hours in a healthcare facility with access to emergency response services following administration.

Loxapine inhalation powder has a boxed warning cautioning of bronchospasms that can potentially lead to respiratory distress and respiratory arrest.

Warnings

All first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs) have warnings regarding neuroleptic malignant syndrome (NMS), which has been reported in association with these agents. All antipsychotics, except loxapine inhalation powder (Adasuve), also share a warning that tardive dyskinesia (TD) may develop in patients treated with these drugs. The risk of TD is higher among the elderly and highest among elderly women.

Leukopenia, neutropenia, and agranulocytosis have been reported with FGAs and SGAs. Patients with a history of a clinically significant low white blood cell count or a drug-induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy. Discontinuation of antipsychotic therapy should be considered if decreases of these cell counts from baseline are experienced.

Extrapyramidal symptoms, specifically dystonias, are associated with use of the FGAs. These symptoms are typically controlled with benztropine and trihexyphenidyl.

SGAs have a warning that hyperglycemia has been reported and, in some cases, the hyperglycemia was extreme and associated with diabetic ketoacidosis (DKA), hyperosmolar coma, or death. There have been reports of hyperglycemia in patients treated with the newest drugs in this class: aripiprazole (Abilify, Abilify Maintena), brexpiprazole (Rexulti), lurasidone (Latuda), paliperidone ER (Invega), paliperidone palmitate (Invega Sustenna, Invega Trinza), and ziprasidone (Geodon). SGAs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. Monitor patients for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. Undesirable alterations in lipid levels have been observed in patients treated with atypical antipsychotics. Significant weight gain has been reported and should be monitored.

Asenapine (Saphris), clozapine, iloperidone (Fanapt), paliperidone ER, paliperidone palmitate, quetiapine, quetiapine XR, and ziprasidone have a warning of QT prolongation and risk of sudden death. The warning states to avoid the use of these drugs in combination with other drugs that are known to prolong the QT interval, in patients with congenital long QT syndrome, and in patients with a history of cardiac arrhythmias. Asenapine had a prolonged QT interval of 2 to 5 msec compared to

placebo. Iloperidone prolongs the QT interval by 9 msec, on average. Paliperidone causes a modest increase in the QT interval (~12 msec). Ziprasidone had an average increase of 20 msec in the QT interval, about 9 to 14 msec longer than risperidone (Risperdal), olanzapine (Zyprexa), quetiapine, and haloperidol, but 14 msec shorter than thioridazine, which has been shown to prolong the QT interval. These products should be avoided in circumstances that may increase the risk of torsades de pointes and/or sudden death including a history of cardiac arrhythmias, such as bradycardia, hypokalemia, hypomagnesemia, and presence of congenital prolongation of the QT interval. The use of quetiapine and clozapine should also be avoided in combination with other drugs that prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class III antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), citalopram (dose dependent), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone). Caution should be exercised when quetiapine and clozapine is prescribed in patients with increased risk of QT prolongation (e.g., cardiovascular disease, family history of QT prolongation, the elderly, congestive heart failure, and heart hypertrophy).

A retrospective cohort study of Medicaid enrollees in Tennessee demonstrated that there is an increased risk of sudden cardiac death for users of first and second generation antipsychotics.[142] The study compared users of typical antipsychotics (n=44,218), second generation antipsychotics (n=46,089), and non-users of antipsychotic drugs (n=186,600). Primary analysis demonstrated that users of typical and second generation antipsychotics had higher rates of sudden cardiac death than non-users, which was demonstrated by the adjusted incidence-rate ratios of 1.99 (95% confidence interval [CI], 1.68 to 2.34) and 2.26 (95% CI, 1.88 to 2.72), respectively. The risk increased correspondingly with increased doses of second generation antipsychotics with the incidence-rate ratio of low doses at 1.59 (95% CI, 1.03 to 2.46) increasing to 2.86 (95% CI, 2.25 to 3.65) for high doses (p=0.01). In contrast, the incidence-rate ratio 1.13 (95% CI, 0.98 to 1.3) of former users of antipsychotic drugs did not demonstrate an increased risk for sudden cardiac death, which demonstrated the risk returns to baseline after the patient discontinues use of the antipsychotics.

Clozapine has a warning regarding a 1% incidence of eosinophilia occurring in patients.

Olanzapine/fluoxetine (Symbyax) has warnings regarding serotonin syndrome, allergic reaction and rash, activation of mania/hypomania, abnormal bleeding, and hyponatremia.

The warnings for olanzapine long-acting injection include the risk of suicide, hyperlipidemia, and weight gain.

Paliperidone has a warning against its use in patients with pre-existing severe gastrointestinal narrowing. Reports of obstructive symptoms in patients with strictures are associated with ingestion of drugs that have non-deformable controlled-release formulations. Because of the design, the drug should only be used in patients who can swallow the tablet whole.

Other warnings for paliperidone include thrombotic thrombocytopenic purpura and antiemetic effect. Risperidone also has a similar warning for antiemetic effect.

Quetiapine XR has warnings for withdrawal symptoms upon discontinuation, the development of cataracts, and risk for hypothyroidism and transaminase elevations. Quetiapine also has a warning regarding risk of cataracts.

Ziprasidone has a warning regarding Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS can be fatal. Ziprasidone should be discontinued if DRESS is suspected.

As a result of pupillary dilation that occurs following the use of many antidepressants, including olanzapine/fluoxetine (Symbyax), an angle-closure attack may occur in a patient with anatomically narrow angles who does not have a patent iridectomy.

Risk Evaluation and Mitigation Strategy (REMS)

Injectable olanzapine (Zyprexa Relprevv) requires the prescriber, pharmacy, and patient to be enrolled in the Zyprexa Relprevv Patient Care Program. Also required are assurances of the implementation of elements to ensure safe use, such as special certification of healthcare providers and dispensing pharmacies, patient registration, and continued monitoring of patients using the injection. Due to the life-threatening risk of agranulocytosis, all clozapine products share a REMS program. The program requires prescribers to be certified to prescribe clozapine, and patients and pharmacies must be enrolled in the clozapine REMS program to ensure safe use. The program provides educational material on agranulocytosis and required neutrophil laboratory monitoring details. Prior to this shared REMS program, prescribers, pharmacies, and patients were required to enroll in each manufacturer's individual monitoring website, which made monitoring continuity difficult when patients changed clozapine formulations.[143] Loxapine inhalation powder (Adasuve) is available only through a restricted program called the Adasuve REMS. Loxapine inhalation powder should only be administered in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation or mechanical ventilation). Wholesalers and distributors must enroll in the program and distribute only to enrolled healthcare facilities.

Warnings

Drug	Elderly Patients with Dementia Psychosis	Suicide	Hyperglycemia	Dyslipidemia	Hyperprolactinemia	Weight Gain	Tardive Dyskinesia	Priapism	Use in Patients with Concomitant Illness	Orthostatic Hypotension	Leukopenia, Neutropenia, Agranulocytosis	QT Prolongation	Seizures	Neuroleptic Malignant Syndrome	Potential for Cognitive and Motor Impairment	Dysphagia	Body Temperature Regulation Disruption	Increases in Blood Pressure in Children and Adolescents	Suicidality in Children and Adolescents
aripiprazole (Abilify)	X	X	X	X	-	X	X	-	X	X	X	-	X	X	X	X	X	-	X
aripiprazole ER (Abilify Maintena)	X	-	X	X	-	X	X	-	X	X	X	-	X	X	X	X	X	-	-
asenapine (Saphris)	X	X	X	X	X	X	X	-	X	X	X	X	X	X	X	X	X	-	-
brexpiprazole (Rexulti)	X	X	X	X	-	X	X	-	-	X	X	-	X	X	X	X	X	-	X
clozapine (Clozaril, Fazaclo, Versacloz)[±]	X	-	X	X	-		X	X	X	X	X	X	X	X	X	X	-	-	-
Iloperidone (Fanapt)	X	X	X	X	X	X	X	X	-	X	X	X	X	X	X	X	X	-	-
loxapine inhalation powder (Adasuve)	X	-	-	-	-	-	-	-	-	X	-	-	X	X	X	-	-	-	-
lurasidone (Latuda)	X	X	X	X	X	X	X	-	X	X	X	-	X	X	X	X	X	-	-
olanzapine oral (Zyprexa)	X	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	X	-	-
paliperidone ER (Invega)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
paliperidone palmitate (Invega Sustenna, Invega Trinza)	X	-	X	X	X	X	X	X	-	X	X	X	X	X	X	X	X	-	-

Warnings (continued)

Drug	Elderly Patients with Dementia Psychosis	Suicide	Hyperglycemia	Dyslipidemia	Hyperprolactinemia	Weight Gain	Tardive Dyskinesia	Priapism	Use in Patients with Concomitant Illness	Orthostatic Hypotension	Leukopenia, Neutropenia, Agranulocytosis	QT Prolongation	Seizures	Neuroleptic Malignant Syndrome	Potential for Cognitive and Motor Impairment	Dysphagia	Body Temperature Regulation Disruption	Increases in Blood Pressure in Children and Adolescents	Suicidality in Children and Adolescents
quetiapine (Seroquel) [¥]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
quetiapine XR (Seroquel XR) [¥]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
risperidone oral (Risperdal) [§]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
ziprasidone oral (Geodon) [#]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
olanzapine/ fluoxetine (Symbyax)	X	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	X	-	-

[¥]Lens changes have been observed in patients using quetiapine long term

[§]Thrombotic Thrombocytopenic Purpura (TTP), antiemetic effect, and increased sensitivity in Parkinson's disease or dementia associated with Lewy bodies are also warnings associated with risperidone

[#]ziprasidone would be discontinued in patients who develop a rash if there is no other identifiable cause

[±]Due to the risk of agranulocytosis, all clozapine products are available only through a restricted program to which prescribers, patients, and pharmacies must enroll; although, clozapine products are not under a REMS program, with the exception of Versacloz, although the risk of agranulocytosis is not different between the products.

DRUG INTERACTIONS[144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174]

Drug	SSRIs	Phenytoin (P)	CYP3A4 Inducer Carbamazepine (C)	CYP3A4 Inhibitors	CYP2D6 Inhibitors
First Generation Antipsychotics					
amitriptyline/ perphenazine	May ↑ concentration of amitriptyline	Causes P levels to fluctuate, amitriptyline may lower seizure threshold	May ↓ concentration of amitriptyline	May ↑ concentration of amitriptyline	May ↑ concentration of amitriptyline
chlorpromazine	--	Causes P levels to fluctuate	--	--	--
fluphenazine	--	Causes P levels to fluctuate	--	--	--
haloperidol	Fluoxetine ↑ concentration of haloperidol	--	Therapeutic effect of haloperidol decreased; may increase C levels	--	--
loxapine inhalation powder (Adasuve)	--	--	--	--	--
molindone (Moban)	--	--	--	--	--
perphenazine	--	Causes P levels to fluctuate	--	--	May ↑ concentration of perphenazine
pimozide (Orap)	Citalopram may additively ↑ QTc values Other SSRIs may↑ concentration of pimozide Contraindicated	--	--	May ↑ concentration of pimozide	May ↑ concentration of pimozide
thioridazine	May ↑ concentration of thioridazine Contraindicated	Causes P levels to fluctuate	--	--	--
thiothixene (Navane)	--	--	--	--	--
trifluoperazine	Fluoxetine and citalopram may prolong QTc	Causes P levels to fluctuate	--	--	--

Drug Interactions (continued)

Drug	SSRIs	Phenytoin (P)	CYP3A4 Inducer	CYP3A4 Inhibitors	CYP2D6 Inhibitors
Second Generation Antipsychotics					
aripiprazole (Abilify) A=aripiprazole	--	--	↓ Cmax and AUC of A; double dose of A	Ketoconazole and itraconazole increase AUC of A; ↓ A dose by half	Quinidine, fluoxetine, paroxetine increase AUC of A; ↓ A dose by half
aripiprazole ER (Abilify Maintena) AER=aripiprazole	--	--	↓ concentration of AER; avoid use for > 14 days	↑ concentration of AER; reduction of AER dose is recommended	↑ concentration of AER; reduction of AER dose is recommended
asenapine (Saphris) [175] A=asenapine	--	--	--	--	May ↓ clearance of A; A may ↓ clearance of substrates
brexpiprazole (Rexulti) B=brexpiprazole	--	--	Exposure of B decreased; double the usual dose of B and further adjust based on clinical response	↑ exposure of B; administer half of the usual B dose	↑ exposure of B; administer half of the usual B dose
clozapine (Clozaril, Fazaclo, Versacloz) C=clozapine	Fluvoxamine ↑ trough concentration of C and its metabolites; consider lower dose of C	P may ↓ C plasma levels	Concomitant use is advised against. Other inducers not recommended, Carbamazepine may increase risk of agranulocytosis	Cimetidine and erythromycin may ↑ plasma levels of C	Use with caution with these agents
iloperidone (Fanapt) I=iloperidone	--	--	--	May ↑ concentration of I	May ↑ concentration of I
lurasidone (Latuda)	--	--	Strong inducers contraindicated May be necessary to increase dose with moderate inducers	Strong inhibitors contraindicated Reduce dose by one-half with moderate inhibitors	--
olanzapine (Zyprexa) O=olanzapine	Fluvoxamine ↑ O AUC; consider lower doses of O	--	CBZ ↑ clearance of O	--	--

Drug Interactions (continued)

Drug	SSRIs	Phenytoin (P)	CYP3A4 Inducer	CYP3A4 Inhibitors	CYP2D6 Inhibitors
Second Generation Antipsychotics *(continued)*					
paliperidone ER (Invega) P=paliperidone	Citalopram can increase QTc prolongation, paroxetine may increase plasma levels of P	--	CBZ ↑ renal clearance of P	--	--
paliperidone palmitate (Invega Sustenna) ± PP=paliperidone palmitate	--	--	With co-administration (e.g., carbamazepine, rifampin, or St John's wort), increase the dose of PP	--	--
paliperidone palmitate (Invega Trinza) ±	--	--	Concomitant use may decrease the exposure of P; avoid using during the 3-month dosing interval, if necessary, consider managing the patient using P	--	--
quetiapine (Seroquel, Seroquel XR) Q=quetiapine	Citalopram and fluoxetine can increase QTc prolongation	P ↑ clearance of Q by 5-fold; increased doses of Q may be needed	Monitor, increased doses of Q may be needed	Ketoconazole ↓ clearance of Q; use caution with Q and all these agents	--
risperidone (Risperdal) R=risperidone	Fluoxetine can increase the plasma level of R	P likely to ↑ clearance of R and active metabolite	CBZ ↑ clearance of R and active metabolite	Itraconazole ↑ levels of R	Paroxetine ↑ levels of R
ziprasidone (Geodon) Z=ziprasidone	Citalopram can increase QTc prolongation	--	CBZ ↓ Z AUC	Ketoconazole ↑ Z AUC	--

The drug-drug interactions of the individual components, fluoxetine (Prozac) and olanzapine (Zyprexa), are applicable to Symbyax.

±Because paliperidone palmitate is hydrolyzed to paliperidone, results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

ADVERSE EFFECTS[176,177,178,179,180,181,182, 183,184,185,186,187 ,188,189,190,191,192,193,194]

Drug	EPS	Glucose Abnormalities	Dyslipidemia	Hypotension	Prolactin Elevation	Sedation	Wt Gain	Anticholinergic Effects	QT Prolongation
First Generation Antipsychotics – Oral									
amitriptyline/ perphenazine	reported	reported	nr	reported	reported	reported	reported	reported	reported
chlorpromazine	reported	reported	nr	reported	reported	reported	reported	Reported	nr
fluphenazine	reported	nr	nr	reported	reported	reported	nr	reported	nr
haloperidol	reported	reported	nr	reported	reported	reported	nr	reported	reported
molindone (Moban)	reported	nr	nr	reported	reported	reported	reported	reported	nr
perphenazine	reported	reported	nr	reported	reported	reported	reported	reported	nr
pimozide (Orap)	reported	nr	nr	nr	0	70	reported	reported	reported
thioridazine	reported	nr	nr	reported	reported	reported	reported	reported	reported
thiothixene (Navane)	reported	reported	nr	reported	reported	reported	reported	reported	nr
trifluoperazine	reported	reported	nr	reported	reported	reported	reported	reported	nr
First Generation Antipsychotics – Injectable									
fluphenazine decanoate	reported	nr	nr	reported	reported	reported	nr	reported	nr
haloperidol decanoate (Haldol Decanoate)	reported	reported	nr	reported	reported	reported	nr	reported	reported

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Adverse Effects (continued)

Drug	EPS	Glucose Abnormalities	Dyslipidemia	Hypotension	Prolactin Elevation	Sedation	Wt Gain	Anticholinergic Effects	QT Prolongation
First Generation Antipsychotics – Inhaled									
loxapine inhalation powder (Adasuve)	nr	nr	nr	0.4	nr	nr	nr	reported	nr
Second Generation Antipsychotics – Oral									
aripiprazole (Abilify)	2-20 (0-3)	reported	reported	reported	reported	4-21 (2-4)	2-3 (1-2)	2-11 (0-7)	nr
asenapine (Saphris)	4-12 (2-7)	reported	reported	nr	reported	13-24 (6-7)	2-5 (<1)	nr	reported
brexpiprazole (Rexulti)	2-14 (0-3)	reported	reported	reported	reported	2-5 (1-3)	2-30 (2-4)	reported	nr
clozapine (Clozaril, Fazaclo, Versacloz)	1-4	reported	reported	9-13	nr	21-39	4	6-31	nr
iloperidone (Fanapt)	4-5 (4)	nr	reported	3-5 (1)	nr	9-15 (5)	1-9 (1)	nr	reported
lurasidone (Latuda)	11 (5)	reported	reported	0.4 (0.2)	reported	22 (10)	reported	2 (<1)	nr
olanzapine oral (Zyprexa)	3-23 (1-13)	2.2-17.4 (3.4-11.5)	21.6-39.6 (9.5-26.1)	3-5 (1-2)	30-47 (7-10.5)	35-48 (9-13)	5-31 (1-9)	4-32 (0-9)	nr
olanzapine/ fluoxetine (Symbyax)[195]	<1	0-37 (0.3-3.6)	8.2-67.8 (1.7-9.9)	4 (1.8)	28 (5)	14 (6)	22-66 (1.8-3)	15 (6)	reported
paliperidone ER (Invega)	3-20 (4-8)	nr	nr	1-4 (1)	reported	6-12 (5-7)	4-9 (1-5)	1-5 (1-2)	reported
quetiapine (Seroquel)	3-12 (1-16)	10.7 (4.6)	4-22 (2-19)	3-7 (1-2)	3.6-13.4 (0-2.6)	18-57 (8-15)	5-23 (0-7)	7-44 (0-13)	reported
quetiapine XR (Seroquel XR)	4-8 (1-5)	7-12 (6)	4-22 (2-19)	3-7 (0-5)	reported	5-14 (4)	1-10 (0-5)	6-40 (1-8)	reported

Adverse Effects (continued)

Drug	EPS	Glucose Abnormalities	Dyslipidemia	Hypotension	Prolactin Elevation	Sedation	Wt Gain	Anticholinergic Effects	QT Prolongation
Second Generation Antipsychotics – Oral *(continued)*									
risperidone oral (Risperdal)	0-18 (0-7)	reported	nr	1-2 (0)	reported	12-67 (4-23)	18 (9)	4-21 (1-8)	reported
ziprasidone oral (Geodon)	14-31 (7-12)	reported	reported	reported	reported	14 (7)	5.6-10 (5.6-4)	4-9 (2-8)	reported

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Drug	EPS	Glucose Abnormalities	Dyslipidemia	Hypotension	Prolactin Elevation	Sedation	Wt Gain	Anticholinergic Effects	QT Prolongation
Second Generation Antipsychotics – Injectable									
aripiprazole IM (Abilify)	2 (0)	nr	nr	nr	nr	3 (2)	nr	nr	nr
aripiprazole ER (Abilify Maintena) *	5 (3)	nr	nr	nr	nr	7 (4)	nr	nr	nr
olanzapine IM (Zyprexa)	1-4 (0)	nr	nr	5	nr	6 (3)	nr	0-2	nr
olanzapine IM (Zyprexa Relprevv)	>5	nr	6.5-24.5	nr	reported	8-13 (7)	5-7 (5)	2-6 (1)	2 (1)
paliperidone palmitate (Invega Sustenna)	0-5 (1)	reported	reported	reported	reported	1-7 (3)	1-4 (1)	reported	nr
paliperidone palmitate (Invega Trinza)	3-6 (1-3)	reported	reported	reported	reported	reported	9.6 (0.7)	reported	nr

Adverse Effects (continued)

Drug	EPS	Glucose Abnormalities	Dyslipidemia	Hypotension	Prolactin Elevation	Sedation	Wt Gain	Anticholinergic Effects	QT Prolongation
Second Generation Antipsychotics – Injectable *(continued)*									
risperidone IM (Risperdal Consta)	4-24 (3-16)	reported	nr	1-2 (0)	<2	5-7 (1-3)	4-7 (1-2)	0-7 (1)	nr
ziprasidone IM (Geodon)	0-2	reported	nr	0-5	reported	8-20	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.
Application site reactions (e.g., blisters, ulcers) have been reported with asenapine (Saphris).
There have been reports of pancreatitis and rhabdomyolysis with quetiapine (Seroquel XR).
*Most notable adverse reaction for Abilify Maintena was akathisia (8%).

Metabolic Effects

Of the second generation antipsychotics (SGAs), clozapine and olanzapine are the agents most frequently associated with weight gain and glucose and lipid abnormalities at therapeutic doses. In a case-control study of 93 patients who were receiving clozapine for schizophrenia or schizoaffective disorder, the prevalence of metabolic syndrome was 54% compared to 21% in the reference group.[196] These adverse effects occur with risperidone and quetiapine, but at a lower frequency than with olanzapine and clozapine. Ziprasidone and aripiprazole have the lowest incidence of these adverse effects.[197,198] These effects can be particularly problematic in patients with schizophrenia as they are likely to have other cardiovascular risk factors, such as smoking, sedentary lifestyle, and unhealthy diet.[199] The relative metabolic effects, including the development of diabetes, of the various SGAs have been demonstrated in several direct comparative clinical trials, prospective studies, and retrospective studies.

The effect of risperidone and olanzapine on body weight and body mass index (BMI) was observed prospectively over a period of 6 months.[200] Significant increases in weight and BMI were apparent in both groups after 3 months of treatment ($p<0.05$). Significant increases in weight continued in both groups throughout the 6-month study, although there was significantly greater weight gain with olanzapine.

In a retrospective chart review of 215 patients taking clozapine, olanzapine, risperidone, quetiapine, haloperidol, or fluphenazine, glucose and lipid levels were evaluated from 2.5 years before and after initiation of the antipsychotic.[201] Glucose levels were increased from baseline for patients treated with clozapine, olanzapine, and haloperidol. All the medications demonstrated statistically significant changes in lipid profile ($p<0.05$), with patients receiving clozapine and olanzapine demonstrating the greatest increase in triglyceride levels.

Another study using Veterans Administration data evaluated patients with schizophrenia on antipsychotic monotherapy who developed diabetes or were hospitalized for ketoacidosis.[202] Of the 56,849 patients identified, 4,132 patients (7.3%) developed diabetes, and 88 patients (0.2%) were hospitalized for ketoacidosis. Clozapine followed by olanzapine demonstrated the highest risk for developing diabetes with hazard ratios of 1.57 and 1.15, respectively, while the risk of developing diabetes risk for quetiapine and risperidone were not significantly different from that for first generation antipsychotics (FGAs), hazard ratios of 1.2 and 1.01, respectively. The study demonstrated the risk of developing diabetes mellitus ranged from 0.05% (risperidone) to 2.03% (clozapine) for patients using SGAs. Though the study demonstrated a small risk to patients taking SGAs, patients with co-morbidities that may add to the risk of developing diabetes should receive periodic monitoring.

Investigators studied 101 patients with schizophrenia or schizoaffective disorder receiving clozapine.[203] In the patient group, the prevalence of diabetes was 25.7%. Mean duration of clozapine treatment was 5.7 years. Logistic regression of the data demonstrated a significant association between diabetes prevalence and Caucasian race ($p=0.02$), and the association between diabetes and family history of diabetes ($p=0.002$); however, significant associations were not demonstrated among diabetes prevalence and BMI or body fat.

A retrospective cohort study compared a cohort of patients with prescription claims for SGAs with a control cohort receiving FGAs, antidepressants, or antibiotics.[204] Investigators found an unadjusted incidence rate for diabetes (new cases per 1,000 per year) of 7.5 for second generation antipsychotics compared to 11.3 for first generation antipsychotics, 7.8 for antidepressants, and 5.1 for antibiotics. The differences among the 3 groups of psychotropic agents were not statistically significant. A further comparison showed the risk of developing diabetes similar in patients receiving clozapine, olanzapine, ziprasidone, thioridazine, and risperidone.

Investigators studied 15,767 Veterans Health Administration patients with schizophrenia who started treatment with olanzapine, quetiapine, risperidone, or haloperidol over a 2-year period.[205] In an adjusted analysis of a follow-up after 1 year, each of the SGAs increased the risk of diabetes by 60 to 70% compared to haloperidol. The hazard ratio (HR) for risk of diabetes for olanzapine was 1.6 (95% confidence interval [CI], 1.2 to 2.2), for quetiapine was 1.7 (95%, CI 1.0 to 2.8), and for risperidone was 1.6 (95% CI, 1.2 to 2.1). The risk of diabetes was higher in patients younger than 50 years of age, as well as for patients receiving olanzapine, quetiapine, or risperidone treatment.

In a similar retrospective review of managed care claims for patients with bipolar disorder, 920 cases of new onset diabetes were case-matched with 5,258 controls.[206] Of the 920 cases, 41% received SGAs, and 34% received FGAs. Compared to FGAs, the HR for risk of diabetes among patients taking clozapine was 7.0 (95% CI, 1.7 to 28.9), for olanzapine was 3.2 (95% CI, 2.7 to 3.8), for quetiapine was 1.8 (95% CI, 1.4 to 2.4), and for risperidone was 3.4 (95% CI, 2.8 to 4.2). These results demonstrate that there is an increased risk of new onset diabetes for patients receiving clozapine, olanzapine, quetiapine, and risperidone.

Adverse metabolic effects of the SGAs have been documented in the pediatric population. Recent literature reviews suggest that significant weight gain may occur in 50 to 60% of children treated with SGAs, and this patient group may be particularly susceptible to developing type 2 diabetes.[207,208] In a blinded, randomized, controlled trial of 39 children, ages 10 to 17 years, SGA-induced weight gain was virtually eliminated by concurrent administration of metformin.[209]

Furthermore, medical records (from 1996 through 2007) of Tennessee Medicaid patients ages 6 to 24 were examined in a large, retrospective study. [210] The cohort included 28,858 children and youth who had recently initiated antipsychotic therapy. The study showed patients on atypical antipsychotics risperidone, quetiapine, aripiprazole, and olanzapine had a 3-fold increased risk of developing type 2 diabetes within the first year of taking these drugs than did propensity score-matched controls (HR=2.49; 95% CI, 1.27 to 4.88). The risk of type 2 diabetes increased with cumulative dose.

SPECIAL POPULATIONS[211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229]

Pediatrics

Molindone (Moban), perphenazine, and thiothixene (Navane) are not recommended in children under the age of 12 years. Trifluoperazine is indicated for the treatment of schizophrenia in children 6 to 12 years old. The safety and effectiveness of any form of fluphenazine have not been established in patients younger than 5 years. Haloperidol should not be used in patients 3 years of age or younger. Pimozide (Orap) and thioridazine should not be used in patients under 2 years of age. Chlorpromazine is not for use in children younger than 6 months. Safety and effectiveness of haloperidol decanoate (Haldol Decanoate) in pediatric patients have not been established.

Aripiprazole oral (Abilify) is approved for treatment of schizophrenia in adolescents aged 13 to 17 years of age. Aripiprazole oral is also indicated as adjunctive or monotherapy for treatment of acute manic or mixed episodes associated with bipolar I disorder in pediatric patients aged 10 to 17 years and for treatment of irritability associated with autistic disorder in children and adolescents aged 6 to 17 years of age.

Paliperidone (Invega) is approved for treatment of schizophrenia in adolescents aged 12 to17 years of age.

Olanzapine (Zyprexa) is approved for treatment of schizophrenia in adolescents aged 13 to 17 years of age and as monotherapy in children and adolescents aged 13 to 17 years for the treatment of acute manic or mixed episodes associated with bipolar I disorder. Compared to adults, adolescents taking olanzapine experienced a greater incidence of adverse effects.

Quetiapine (Seroquel, Seroquel XR) is approved for treatment of schizophrenia in adolescents aged 13 to 17 years of age and for treatment of mania associated with bipolar disorder in patients 10 to 17 years of age. Safety and effectiveness of Seroquel XR are supported by studies of Seroquel for schizophrenia in adolescent patients 13 to 17 years of age and in bipolar mania in children and adolescent patients 10 to 17 years of age.

Risperidone (Risperdal) is approved for treatment of schizophrenia in adolescents aged 13 to 17 years of age, as monotherapy in children and adolescents aged 10 to 17 years for the treatment of acute manic or mixed episodes associated with bipolar I disorder, and for treatment of irritability associated with autistic disorder in children and adolescents aged 5 to 16 years of age.

Safety and effectiveness of asenapine (Saphris), iloperidone (Fanapt), loxapine inhalation powder (Adasuve), lurasidone (Latuda), clozapine, olanzapine (Zyprexa), ziprasidone (Geodon), olanzapine/fluoxetine (Symbyax), and the injectable products in pediatric patients have not been established.

Autistic Disorder / Pervasive Developmental Disorder (PDD)

Efficacy Scales

ABC (Aberrant Behavior Checklist) – This scale is a 58-item third-party informant rating scale originally developed to monitor an array of behavioral features among patients with mental retardation. It relies on clinical observations of activity and behavior and has been validated in children with concomitant autistic and psychotic disorders.[230,231]

CARS (Childhood Autism Rating Scale) – This is the most widely used standardized instrument specifically designed to aid in the diagnosis of autism in children as young as 2 years of age. This scale includes items from 5 prominent systems for diagnosing autism. Each item covers a particular characteristic, ability, or behavior. This test combines parent reports and direct observation by a professional.[232]

NCBRF (Nisonger Child Behavior Rating Form) – This is a standardized instrument for assessing child and adolescent behavior. There are 2 levels of this form; one of these is for children with developmental disabilities, specifically mental retardation and/or autism spectrum disorders. There is 1 version of the form for completion by parents and 1 for completion by teachers.[233]

risperidone (Risperdal)

Investigators conducted a multicenter, randomized, double-blind trial comparing risperidone to placebo for the treatment of autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior in 101 children (ages 5 to 17 years).[234] Treatment with risperidone for 8 weeks (dose 0.5 to 3.5 mg/day) resulted in a 57% reduction in the Irritability score, as compared with a 14% decrease in the placebo group ($p<0.001$). The rate of CGI-I response was 69% in the risperidone group and 12% in the placebo group ($p<0.001$). Risperidone therapy was associated with an average weight gain of 2.7 kg, as compared with 0.8 kg with placebo ($p<0.001$). Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group than in the placebo group ($p<0.05$ for each comparison). In two-thirds of the responders, the benefit was maintained at 6 months.

In an 8-week, randomized, double-blind trial, risperidone or placebo solution (0.01 to 0.06 mg/kg/day) was administered to 79 children (ages 5 to 12 years) with pervasive developmental disorders (PDD).[235] Subjects who were taking risperidone (mean dosage 1.17 mg/day) experienced a 64% improvement on the primary endpoint of irritability subscale of the ABC compared with 31% of those taking placebo ($p<0.05$). Risperidone-treated subjects also exhibited significantly greater decreases on the other subscales of the ABC, conduct problem, insecure/anxious, hyperactive, and overly sensitive subscales of the NCBRF, and on the VAS of the most troublesome symptom. More risperidone-treated subjects (87%) showed improvement in CGI compared with the placebo-treated group (40%; $p<0.05$). Somnolence, the most frequently reported adverse event, was noted in 72.5 and 7.7% of subjects receiving risperidone and placebo, respectively ($p<0.05$). Risperidone-treated subjects experienced greater increases in weight, pulse rate, and systolic blood pressure than those in the placebo-treated group. Extrapyramidal symptoms scores were comparable between groups.

Forty children, ages 2 to 9 years, with autism were randomized to receive risperidone 1 mg or placebo daily for 6 months.[236] Improvement in CARS was noted in 63% of children receiving risperidone and none of the children receiving placebo ($p<0.001$). CGAS improved in 89% of patients receiving the active treatment and 10% receiving placebo ($p=0.035$). Risperidone also improved social responsiveness and nonverbal communication, and reduced the symptoms of hyperactivity and aggression. Risperidone was associated with mild weight gain, sedation, and dyskinesias.

aripiprazole (Abilify)

In an 8-week, placebo-controlled trial, 98 children and adolescents diagnosed with autism (aged 6 to 17 years), received doses of aripiprazole (2 mg to 15 mg/day) or placebo.[237] Efficacy was measured using the Aberrant Behavior Checklist (ABC)-irritability scale and the Clinical Global Impression-Improvement (CGI-S) scale. The ABC-I subscale measured the emotional and irritability associated with autistic disorder, including aggression towards others, deliberate self-injurious behavior, temper tantrums, and quickly changing moods. At the end of the 8-week trial, improvements were significant in the ABC-I and CGI-I scales, with the mean daily dose of aripiprazole of 8.6 mg/day.

The second 8-week, placebo-controlled trial included 218 children and adolescents diagnosed with autism were treated with 3 fixed doses of aripiprazole (5 mg/day, 10 mg/day or 15 mg/day) compared to placebo.[238] Aripiprazole was started at 2 mg/day and increased to 5 mg/day after 1 week. The other groups were increased to 10 mg/day and 15 mg/day the next 2 consecutive weeks. At the end of the 8-week trial, all 3 doses of aripiprazole showed significantly improved scored on the ABC-I subscale compared to placebo.

Bipolar Disorder

aripiprazole (Abilify)

Patients (n=296) ages 10 to 17 years with bipolar I disorder with current manic or mixed episodes, with or without psychotic features, and a Young Mania Rating Scale (YMRS) score $\geq$ 20 were enrolled in a randomized, multicenter, double-blind 4-week study.[239] The primary endpoint was change from baseline in the YMRS total score. Both doses of aripiprazole were superior to placebo on the YMRS total score beginning at week 1 and continuing through week 4. Response ($\geq$ 50% reduction in YMRS total score) at week 4 was achieved by 44.8, 63.6, and 26.1% of subjects in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo groups, respectively ($p<0.01$ for both doses versus placebo). Common adverse effects included EPS and somnolence; rates were higher for aripiprazole 30 mg compared with aripiprazole 10 mg. Weight gain was not significantly different between the aripiprazole 10 mg (+0.82 kg) or 30 mg (+1.08 kg) groups compared with the placebo group (+0.56 kg) ($p=0.35$ and $p=0.13$, respectively).

quetiapine XR (Seroquel XR)

The safety and efficacy of quetiapine XR in adolescents with mania associated with bipolar I disorder were supported by a 3-week, double-blind, placebo-controlled multicenter trial with quetiapine.[240] Quetiapine at doses of 400 and 600 mg/day were superior to placebo in the reduction of YMRS total score in adolescent patients (n=277) aged 10 to 17 years. The adverse event profile of quetiapine was mild to moderate and similar to what is seen in adult bipolar patients.

Schizophrenia

aripiprazole (Abilify)

Investigators evaluated the efficacy of aripiprazole in a 6-week, randomized, double-blind, multicenter, placebo-controlled study of patients ages 13 to 17 years of age (n=302) who met DSM-IV criteria for schizophrenia and had a PANSS greater than or equal to 70 at baseline.[241] Patients were randomized to receive oral aripiprazole 10 mg/day, aripiprazole 30 mg/day, or placebo. Patients were randomized to receive aripiprazole started at 2 mg/day and titrated to 10 mg/day after 5 days or 30 mg/day after 11 days. Each treatment arm was continued on the final dose for 6 weeks total. The primary outcome measure of the study indicated that oral aripiprazole (10 mg/day and 30 mg/day) leads to better symptom control of schizophrenia over placebo based on a greater reduction in the PANSS total score. Other study results demonstrated that patients receiving aripiprazole 10 mg/day or 30 mg/day had greater improvements in the PANSS positive subscale and Clinical Global Impression-Severity and Clinical Global Impression-Improvement scale scores than the placebo recipients. In addition, the study demonstrated that aripiprazole 10 mg/day had greater improvement versus placebo in the PANSS negative subscale score. The study did not demonstrate a significant difference in efficacy between the 10 mg/day dose and the 30 mg/day dose of aripiprazole. Investigators reported patients receiving aripiprazole had a clinically significant increase in weight based on the U.S. FDA definition (increase ≥ 7%). Weight gain was demonstrated at both doses and was greater than placebo; weight gain was demonstrated in 4% of patients receiving aripiprazole 10 mg/day, 5.2% of patients treated with 30 mg/day, and 1% of patients in the placebo arm. Despite the weight gain, aripiprazole was reported by investigators as well tolerated in the study patients, with most adverse events being reported mild to moderate in severity.

molindone (Moban), olanzapine (Zyprexa), and risperidone (Risperdal)

A double-blind trial randomly assigned pediatric patients with early-onset schizophrenia and schizoaffective disorder to treatment with either oral olanzapine (2.5-20 mg/day), risperidone (0.5-6 mg/day), or molindone (10-140 mg/day plus 1 mg/day of benztropine) for 8 weeks.[242] The primary outcome was response to treatment, defined as a CGI improvement score of 1 or 2 and $\geq$20% reduction in PANSS total score. Of 119 randomly assigned to treatment, 116 received at least 1 dose of treatment and thus were available for analysis. No significant differences were found among treatment groups in response rates (molindone: 50%; olanzapine: 34%; risperidone: 46%) or magnitude of symptom reduction. Olanzapine and risperidone were associated with significantly greater weight gain. Molindone was associated with more akathisia.

paliperidone ER (Invega)

A 6-week, double-blind, parallel-group study, randomized adolescents (n=201), 12 to 17 years old with schizophrenia, to receive either placebo or 1 of 3 weight-based, fixed doses of paliperidone ER, once-daily (patients weighing 29 to < 51 kg at baseline: 1.5 mg [Low], 3 mg [Medium], or 6 mg [High]; patients weighing ≥ 51 kg: 1.5 mg [Low], 6 mg [Medium], or 12 mg [High]).[243] The PANSS demonstrated overall efficacy of paliperidone ER in adolescents with schizophrenia in the dose range of 3 to 12 mg/day. Although doses within this broad range were shown to be effective, there was no clear benefit to efficacy at the higher doses.

quetiapine (Seroquel)

In a 6-week, double-blind, placebo-controlled trial, adolescents (n=222), 13 to 17 years old with schizophrenia were randomized to quetiapine 400 or 800 mg per day, or placebo.[244] Both doses of quetiapine were superior to placebo in reducing PANSS total score.

quetiapine XR (Seroquel XR)

The safety and efficacy of quetiapine XR in adolescents with schizophrenia were supported by a 6-week, double-blind, placebo-controlled trial with quetiapine.[245] Quetiapine at doses of 400 and 800 mg/day provided significant improvements in symptoms associated with schizophrenia in adolescent patients (n=220) aged 13 to 17 years, including the primary efficacy measure of PANSS total score change. The adverse event profile of quetiapine was well tolerated and similar to what is seen in adult schizophrenia patients.

Pregnancy

Clozapine and lurasidone are Pregnancy Category B. All other antipsychotics are Pregnancy Category C.

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery.[246] There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while, in some cases, symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization. These products should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Geriatrics

Elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo when treated with any antipsychotic. The cause of reported death in elderly patients treated with SGAs varies. Most deaths appeared to be either cardiovascular or infectious.

Clinical studies with clozapine did not include sufficient numbers of subjects over 65 years of age to determine if their response differs from that of younger subjects. Elderly patients may be more susceptible to the possible cardiovascular adverse effects of clozapine, including orthostatic hypotension and tachycardia, and to its anticholinergic effects, such as urinary retention and constipation. Some clinical experience suggests that the prevalence of tardive dyskinesia with clozapine treatment appears highest among the elderly, especially elderly women.

Hepatic Impairment

Caution is recommended in patients using clozapine who have concurrent hepatic disease. Hepatitis has been reported in both patients with normal and pre-existing liver function abnormalities. Liver function tests should be performed immediately in patients on clozapine who develop nausea, vomiting, and/or anorexia. Treatment should be discontinued if elevation of these values is clinically relevant or if symptoms of jaundice occur.

Paliperidone ER (Invega) has not been studied in severe hepatic impairment. No dosage adjustment of Invega is recommended in mild to moderate hepatic impairment. Paliperidone palmitate (Invega Sustenna and Invega Trinza) has not been studied in patients with hepatic impairment.

Since quetiapine (Seroquel, Seroquel XR) is extensively metabolized by the liver, higher plasma levels are expected in the hepatically-impaired population, and dosage adjustment may be needed.

Risperidone doses should be decreased in patients with hepatic disease.

Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of olanzapine/fluoxetine (Symbyax) may be altered in patients with hepatic impairment.

Asenapine (Saphris) is not recommended in patients with severe hepatic impairment.

Dosing of lurasidone should not exceed more than 40 mg daily in patients with moderate or severe hepatic impairment.

For mild hepatic impairment, no dose adjustment is required with iloperidone (Fanapt). For moderate hepatic impairment, caution should be exercised. Iloperidone is not recommended for severe hepatic impairment.

Patients with moderate to severe hepatic impairment experienced higher exposure to brexpiprazole (Rexulti) than patients with normal hepatic function. The maximum recommended dosage should be reduced in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7).

Renal Impairment

Dosing of lurasidone should not exceed more than 40 mg daily in patients with moderate or severe renal impairment.

Dosing for paliperidone ER (Invega, Invega Sustenna) must be individualized according to renal function status. The use of paliperidone palmitate (Invega Sustenna, Invega Trinza) is not recommended in patients with moderate to severe renal impairment (CrCl < 50 mL/min).

Risperidone doses should be decreased in patients with renal disease.

Patients with impaired renal function experienced higher exposure to brexpiprazole (Rexulti) than patients with normal renal function. The maximum recommended dosage should be reduced in patients with moderate, severe, or end-stage renal impairment (CrCl <60 mL/minute).

Jewish Background

A disproportionate number of cases of clozapine-related agranulocytosis in patients of Jewish descent have been reported.

Smoking

Tobacco smoke may decrease clozapine (Clozaril, FazaClo, Versacloz) plasma levels, resulting in a decrease in effectiveness of a previously effective dose. Olanzapine clearance is approximately 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended. Smoking is not expected to have an effect on the pharmacokinetics of aripiprazole (Abilify), asenapine (Saphris), iloperidone (Fanapt), loxapine inhalation powder (Adasuve), lurasidone (Latuda), quetiapine (Seroquel, Seroquel XR), paliperidone ER (Invega), and ziprasidone (Geodon).

DOSAGES – ADULTS[247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274]

Drug	Schizophrenia/Psychotic Disorders		Other Indications	Dosage Forms
	Initial Dose	Usual Maintenance Dose		
First Generation Antipsychotics				
amitriptyline/ perphenazine	25/2-50/8 mg 3 to 4 times daily	Stable dose 2 to 4 times daily	--	Tablets: 10/2, 10/4, 25/2, 25/4, 50/4 mg
chlorpromazine	25 mg 3 times daily	Up to 1,000 mg daily	25-100 mg 3 or 4 times daily	Tablets: 10, 25, 50, 100, 200 mg
fluphenazine	Oral: 2.5-10 mg 3 to 4 times daily IM/SC: 12.5-25 mg, injection may control symptoms for 4 to 6 weeks	Oral: 1-5 mg daily IM/SC: 50 mg every 1 to 4 weeks as needed/tolerated	--	Tablets: 1, 2.5, 5, 10 mg Elixir: 2.5 mg/5 mL, 5 mg/mL; Vials: 25 mg/mL
haloperidol	Oral: 0.5-2 mg 2 to 3 times daily IM: 10-15 times the oral dose, generally every 4 weeks*	Up to 100 mg daily for tablets and elixir; 20 mg daily for lactate injection; 450 mg per month for decanoate	0.5-1.5 mg 3 times daily (Tourette's); 0.05-0.075 mg/kg/day (behavioral disorders, hyperactivity)	Tablets: 0.5, 1, 2, 5, 10, 20 mg Elixir: 2 mg/mL Vials: (lactate) 5 mg/mL; (decanoate) 50, 100 mg/mL
loxapine inhalation powder (Adasuve)	Oral inhalation: 10 mg; only 1 dose should be administered within a 24-hour period Ω			Single-use inhaler: 10 mg
Molindone (Moban)	50-75 mg in 3 to 4 divided doses	5-25 mg 3 to 4 times daily, up to 225 mg daily	--	Tablets: 5, 10, 25, 50 mg
perphenazine	4-8 mg 3 times daily	Up to 64 mg daily	--	Tablets: 2, 4, 8, 16 mg
pimozide (Orap)	--	--	0.2 mg/kg/day for Tourette's	Tablets: 1, 2 mg
thioridazine	50-100 mg 3 times daily	Up to 800 mg daily	--	Tablets: 10, 25, 50, 100 mg
thiothixene (Navane)	2 mg 3 times daily	Up to 60 mg daily	--	Capsules: 1, 2, 5, 10 mg
trifluoperazine	2-5 mg twice daily	15-20 mg daily	1-2 mg twice daily (non-psychotic anxiety)	Tablets: 1, 2, 5, 10 mg

* Haloperidol decanoate should be administered by deep intramuscular injection. It should only be used in patients who require prolonged parenteral antipsychotic therapy. It is recommended that patients being considered for haloperidol decanoate therapy have been treated with, and tolerate well, short-acting haloperidol in order to reduce the possibility of an unexpected adverse sensitivity to haloperidol.

Ω Loxapine inhalation powder should be administered by a healthcare professional.

Dosages – Adults (continued)

Drug	Other Indications	Schizophrenia		Bipolar Disorder		Dosage Forms
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	
Second Generation Antipsychotics						
aripiprazole (Abilify, Abilify Maintena)	Adjunctive treatment for depression: 2-5 mg daily, maintenance dose 5-10 mg daily (maximum dose: 15 mg daily) Tourette's disorder: <50 kg: initial dose 2 mg daily, maintenance dose 5 mg daily (maximum dose 10 mg daily) ≥50 kg: initial dose 2 mg daily, maintenance dose 10 mg daily (maximum dose 20 mg daily)	10-15 mg once daily IM: 9.75 mg (maximum dose = 30 mg daily) IM (Maintena): 400 mg monthly[#]	10-15 mg once daily Maximum dose = 30 mg/day IM (Maintena): 400 mg IM once monthly based upon tolerability[#]	15 mg once daily IM: 9.75 mg (maximum dose = 30 mg daily) 10 to 15 mg once daily (adjunct to lithium and valproate)[#]	15 mg once daily Maximum dose = 30 mg/day	Tablets: 2, 5, 10, 15, 20, 30 mg Orally disintegrating tablets†: 10, 15 mg Oral solution†: 1 mg/mL Maintena: 300 mg/vial and 400 mg/vial of lyophilized powder for reconstitution
asenapine (Saphris)	--	Acute: 5 mg twice daily Maintenance: 5 mg twice daily	Acute:5 mg twice daily Maximum dose = 10 mg twice daily Maintenance: 10 mg twice daily Maximum dose = 10 mg twice daily	Acute: 10 mg twice daily as monotherapy 5 mg twice daily (adjunct to lithium and valproate)	5-10 mg twice daily Maximum dose = 10 mg twice daily 5 - 10 mg twice daily (adjunct to lithium and valproate) Maximum dose = 10 mg twice daily	Sublingual tablets: 2.5, 5, 10 mg
brexpiprazole Rexulti	Adjunctive treatment of major depressive disorder: starting 0.5 mg or 1 mg once daily, target dose 2 mg once daily, maximum 3 mg daily	1 mg once daily on Days 1 to 4	2 to 4 mg once daily Maximum dose = 4 mg daily	--	--	Tablets: 0.25, 0.5, 1, 2, 3, 4 mg

Dosages – Adults (continued)

Drug	Other Indications	Schizophrenia		Bipolar Disorder		Dosage Forms
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	
Second Generation Antipsychotics *(continued)*						
clozapine (Clozaril)	--	12.5 mg once or twice daily	Target: 300 – 450 mg/day Maximum dose= 900 mg/day	--	--	Tablets: 25, 50, 100, 200 mg
clozapine (Fazaclo)	--			--	--	ODT: 12.5, 25, 100, 150, 200 mg
clozapine (Versacloz)	--			--	--	Suspension: 50 mg/mL in 100 mL bottles
lurasidone (Latuda)	--	40 mg once daily with food	40-160 mg once daily with food Maximum dose= 160 mg/day	20 mg once daily with food	20-120 mg once daily with food Maximum dose= 160 mg/day	Tablets: 20, 40, 60, 80, 120 mg
iloperidone (Fanapt)	--	1 mg twice daily	12-24 mg twice daily	--	--	Tablets: 1, 2, 4, 6, 8, 10, 12 mg Titration pack: 2 each of 1, 2, 4, and 6 mg tablets

[#]Abilify Maintena should only be administered by a healthcare professional as an intramuscular injection in the deltoid or gluteal muscle. Administer no sooner than 26 days after the previous injection; continue treatment with oral aripiprazole (10 mg to 20 mg) or other oral antipsychotic for 14 consecutive days to maintain therapeutic antipsychotic concentrations during initiation of therapy. If transitioning from another depot injection, administer Abilify Maintena in place of the next scheduled injection. No oral supplementation should be required.

[†]Otsuka has discontinued brand Abilify Discmelt 10 mg oral disintegrating tablets. The company has also discontinued the oral solution and injection. The 15 mg ODT tablets are still available, but supply is expected to be depleted by November 2015.

Dosages – Adults (continued)

Drug	Other Indications	Schizophrenia		Bipolar Disorder		Dosage Forms
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	
Second Generation Antipsychotics *(continued)*						
olanzapine (Zyprexa, Zyprexa Relprevv)	--	5-10 mg once daily IM (short-acting): 2.5-10 mg IM (long-acting): 150-300 mg every 2 weeks or 300-405 mg every 4 weeks±	10 mg once daily IM (short-acting): up to 30 mg daily±	Manic or mixed: 10-15 mg once daily IM (short-acting): 2.5-10 mg±	Manic or mixed: 5-20 mg once daily IM (short-acting): Up to 30 mg daily±	Tablets: 2.5, 5, 7.5, 10, 15, 20 mg ODT: 5, 10, 15, 20 mg Vial (short-acting): 10 mg Vial (long-acting): 210, 300, 405 mg
paliperidone ER (Invega) paliperidone palmitate (Invega Sustenna, Invega Trinza) ◊	Schizoaffective disorder: initial 6 mg/day, maintenance 3-12 mg/day (maximum 2 mg/day) IM (Invega Sustenna): initial 234 mg/day then 156 mg/day on day 8, maintenance 78-234 mg/day (maximum 234 mg/day) IM (Invega Trinza): once every 3 months; dose dependent upon previous dose of Invega Sustenna (see label)	6 mg once daily Invega Sustenna IM: 234 mg IM on day 1, then 156 mg IM 1 week laterß	3-12 mg once daily (maximum dose = 12mg/day) Invega Sustenna IM: 117 mg monthlyß	--	--	Tablets: 1.5, 3, 6, 9 mg Invega Sustenna Injection: 39, 78, 117, 156, 234 mg Invega Trinza Injection: 273, 410, 546, 819 mg

± Zyprexa Relprevv is intended for deep intramuscular gluteal injection only and should be administered by a healthcare professional.

◊ Invega Sustenna and Invega Trinza are intended for intramuscular use into the deltoid or gluteal muscle only by a health care professional.

ßThe first and second initiation doses of Invega Sustenna must be administered in the deltoid muscle. Monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

Dosages – Adults (continued)

Drug	Other Indications	Schizophrenia		Bipolar Disorder		Dosage Forms
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	
Second Generation Antipsychotics *(continued)*						
quetiapine (Seroquel)[275,276]	Bipolar depression Initial 50 mg/day, maintenance 300mg/day, maximum 300 mg/day	25 mg twice daily	150-750 mg/day; divided into 2 to 3 doses	50 mg twice daily	400-800 mg/day	Tablets: 25, 50, 100, 200, 300, 400 mg
quetiapine, ER (Seroquel XR)[277]	Major depressive disorder in combination with antidepressants: initial 50 mg/day, recommended 150 – 300 mg/day Depressive episodes associated with bipolar disorder: initial 100 mg/day, recommended 300 mg/day	300 mg in the evening	400-800 mg/day	300 mg in the evening	400-800 mg/day	ER tablets: 50, 150, 200, 300, 400 mg
risperidone (Risperdal, Risperdal Consta)[278,279]		1 mg twice daily IM: 25 mg every 2 weeks¥	4-8 mg/day IM: 50 mg every 2 weeks¥	2-3 mg once daily IM: 25 mg every 2 weeks¥	1-6 mg/day IM: 50 mg every 2 weeks¥	Tablets: 0.25, 0.5, 1, 2, 3, 4 mg ODT: 0.25, 0.5, 1, 2, 3, 4 mg Oral solution: 1 mg/mL Syringes: 12.5, 25, 37.5, 50 mg
ziprasidone (Geodon)[280]	--	20 mg twice IM: 10-20 mg	40-80 mg twice daily IM: Up to 40 mg daily for 3 consecutive days	40 mg twice daily	40-80 mg twice daily	Capsules: 20, 40, 60, 80 mg Vial: 20 mg
olanzapine/ fluoxetine (Symbyax)[281]	Treatment-resistant depression: 6/25 mg daily in evening	--	--	6/25 mg daily in evening	6/25-12/50 mg daily in evening	Capsules: 3/25, 6/25, 6/50, 12/25, 12/50 mg

¥Risperdal Consta should be administered by deep intramuscular deltoid or gluteal injection by a health care professional.

DOSAGES – PEDIATRICS[282,283,284,285,286,287,288,289,290,291,292,293,294,295]

Drug	Other Indications	Schizophrenia		Bipolar Disorder	
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose
First Generation Antipsychotics					
chlorpromazine	0.5 mg/kg 2 to 3 hours before operation (preoperative apprehension)	0.5 mg/kg every 4 to 6 hours	Up to 200 mg daily	--	--
fluphenazine	--	0.25 mg 1 to 4 times daily	0.25-0.75 mg 1 to 4 times daily	--	--
haloperidol	0.05-0.075 mg/kg/day (Tourette's, behavior disorders/hyperactivity)	0.5 mg daily	0.15 mg/kg/day in divided doses	--	--
pimozide (Orap)	0.05 mg/kg/day up to 0.2 mg/kg/day (Tourette's)	--	--	--	--
thioridazine	--	0.5 mg/kg/day in divided doses	3 mg/kg/day in divided doses	--	--
trifluoperazine	--	1 mg once or twice daily	Up to 15 mg daily	--	--

Dosages – Pediatrics (continued)

Drug	Irritability associated with Autistic Disorder		Schizophrenia		Bipolar Disorder	
	Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose
Second Generation Antipsychotics						
aripiprazole (Abilify)	Age 6-17 years: 2 mg daily	Age 6-17 years*: 5-10 mg daily Maximum dose = 15 mg daily	Age 13-17 years: 2 mg daily	Age 13-17 years: 10 mg daily Maximum dose = 30 mg daily	Age 10-17 years: 2 mg daily	Age 10-17 years: 10 mg daily Maximum dose = 30 mg daily
asenapine (Saphris)	--	--	--	--	Age 10-17 years: 2.5 mg twice daily	Age 10-17 years: 2.5-10 mg twice daily Maximum dose = 10 mg twice daily
olanzapine (Zyprexa)	--	--	Age 13-17 years: 2.5-5 mg daily	Age 13-17 years: 10 mg daily	Age 13-17 years: 2.5-5 mg daily	Age 13-17 years: 10 mg daily
paliperidone (Invega)	--	--	Age 12-17 years: Weight < 51 kg: 3 mg daily Weight ≥ 51 kg: 3 mg daily	Age 12-17 years: Weight < 51 kg: 3 to 6 mg daily Maximum dose = 6 mg daily Weight ≥ 51 kg: 3 to 12 mg daily Maximum dose =12 mg daily	--	--
quetiapine (Seroquel)	--	--	Age 13-17 years: 25 mg twice daily	Age 13-17 years: 400-800 mg per day	Age 10-17 years: 25 mg twice daily	Age 10-17 years: 400-600 mg per day
quetiapine (Seroquel XR)	--	--	Age 13-17 years: 50-400 mg per day	Age 13-17 years: 400-800 mg per day	Age 10-17 years: 50-400 mg per day	Age 10-17 years: 400-600 mg per day
risperidone (Risperdal)	Age ≥5 years: Weight <20 kg: 0.25 mg daily Weight ≥20 kg: 0.5 mg daily	Age ≥5 years: Weight <20 kg: 0.5 mg daily after at least 4 days Weight ≥ 20 kg: 1 mg daily after at least 4 days Maintain for at least 14 days. If insufficient response, increase by 0.25 mg per day for weight <20 kg or 0.5 mg per day for weight ≥20 kg	Age 13-17 years: 0.5 mg daily	Age 13-17 years: 3 mg daily	Age 10-17 years: 0.5 mg daily	Age 10-17 years: 2.5 mg daily

* The efficacy of aripiprazole for the maintenance treatment of irritability associated with autistic disorder was not established. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

Dosing Considerations

The initial quetiapine (Seroquel) dose should be 25 mg once daily in patients with hepatic impairment. For dosing of quetiapine XR (Seroquel XR) in patients with hepatic impairment, dosing begins at 50 mg daily. Quetiapine XR should be administered either without food or with a light meal.

The dose of paliperidone ER (Invega) should be reduced in patients with moderate or severe renal impairment as its clearance is reduced by 64 to 71%.

The initial risperidone (Risperdal) dose should be reduced to 0.5 mg twice daily in patients who are elderly, debilitated, have severe renal or hepatic impairment, or are prone to hypotension.

Lurasidone (Latuda) and ziprasidone (Geodon) should be given with food. A snack or meal of at least 350 calories is recommended for lurasidone.

Do not swallow asenapine (Saphris) sublingual tablets. They should be placed under the tongue and left to dissolve completely. Patients taking asenapine (Saphris) should not ingest food or water for 10 minutes following a dose.

The dose of iloperidone (Fanapt) should be reduced by one-half for patients who are taking CYP2D6 or 3A4 inhibitors.

The starting dose of olanzapine/fluoxetine (3 mg/25 mg to 6 mg/25 mg) should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine/fluoxetine. These factors include female gender, geriatric age, non-smoking status, or those patients who may be pharmacodynamically sensitive to olanzapine. Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. When indicated, dose escalation should be performed with caution in these patients.

Prior to administering loxapine inhalation powder (Adasuve), all patients should be screened for a history of pulmonary disease, and examined (including chest auscultation) for respiratory abnormalities (e.g., wheezing). After administration, patients should be monitored for signs and symptoms of bronchospasm. Again, a physical examination, including chest auscultation, should be performed at least every 15 minutes for at least one hour.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Studies of less than 4 weeks' duration were excluded since this short time frame may be insufficient to appropriately evaluate the effects of antipsychotic agents. Studies focusing specifically on the elderly population (≥65 years) or on inpatients were excluded because they are not applicable to the patient population under consideration. Studies that did not use the standard rating scales described below were also excluded. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Psychotic Disorders

Efficacy Scales for Psychotic Disorders

The 2 scales most commonly used for measuring symptom reduction of schizophrenia patients in clinical trials are the BPRS and PANSS.

BPRS (Brief Psychiatric Rating Scale) – This is a 16-item scale with 9 general symptom items, 5 positive-symptom items and 2 negative-symptom items. It is completed by the physician with each item scored on a 7-point severity scale.[296]

PANSS (Positive and Negative Syndrome Scale) – This is a 30-item scale with 16 general psychopathology symptom items, 7 positive-symptom items, and 7 negative symptom items. The physician completes this scale by scoring each item on a 7-point severity scale. The positive- and negative-symptom item groups are often reported separately.[297]

Other scales are also used, depending on the specific outcomes being studied.

CGI-I (Clinical Global Impression – Global Improvement) – This 3-item scale assesses the patient's improvement or worsening by comparing a patient's baseline condition with his or her current condition.[298]

CGI-S (Clinical Global Impression – Severity) – This 3-item scale assesses the clinician's impression of the current state of the patient's illness and provides an assessment of the patient's current symptom severity. The rater is asked to consider his total clinical experience with the given population.[299]

HRQOL (Health Related Quality Of Life) – HRQOL includes measurements of physical and social function, psychological status, functional capacity, somatic sensation, and the sense of well-being impacted by health status.

MADRS (Montgomery Asberg Depression Rating Scale) – This scale measures the effect of treatment on depression severity and, as such, requires a baseline assessment before treatment with subsequent assessments during the course of treatment. The MADRS measures the severity of a number of symptoms, including mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation, and restlessness.[300]

MLDL (Munich Life Quality Dimension List) – This scale measures subjective quality of life (QoL) by having subjects respond in terms of both satisfaction and importance on a 0-10 scale. This is an instrument for cognitive assessment of elementary components (physical condition, psyche, social life, everyday life) of quality of life.

NSA-16 (Negative Symptom Assessment) – The NSA-16 was developed to evaluate the presence and severity of negative symptoms of schizophrenia. This assessment is a multidimensional structure consisting of 5 factors: communication, emotion/affect, social involvement, motivation, and retardation.[301]

PEC (Positive and Negative Syndrome Scale-Excited Component) – This is an investigator-rated instrument consisting of 5 items: poor impulse control, tension, hostility, uncooperativeness, and excitement. Each item is scored on a scale from 1 (absent) to 7 (extreme). The total PEC score can range from 5 to 35.

PHQ-9 (9-item Patient Health Questionnaire) – This is a self administered version of PRIME-MD instrument commonly used for mental disorders.[302] Depression symptoms are self reported and range from 0 (not at all), to 3 (nearly every day). The questions incorporate diagnostic criteria associated with depression as identified in the DSM-IV.

QIDS-SR (Depressive Symptomatology-Self-Report) – This self assessment scale was developed from the 30-item Inventory of Depressive Symptomatology (IDS).[303] All criteria are based on the DSM-IV criterion for major depressive disorder. This assessment has been validated to have similar sensitivity to both the HAM-D and the IDS-SR.

SANS (Scale for the Assessment of Negative Symptoms) – This scale assesses 5 symptom complexes to obtain clinical ratings of negative symptoms in patients with schizophrenia. These symptom complexes are affective blunting, alogia (impoverished thinking), avolition/apathy, anhedonia/asociality, and disturbance of attention.[304]

SAPS (Scale for the Assessment of Positive Symptoms) – This scale is designed to assess positive symptoms, primarily those that occur in schizophrenia.[305]

SWN (Subjective Well-Being under Neuroleptic Treatment Scale) – This subjective scale is mainly influenced by psychopathological status in patients receiving second generation antipsychotics (SGAs). SWN has been shown to significantly correlate with the PANSS.[306]

VAS (Visual Analog Scale) – The VAS is one of the most frequently used measurement scales in health care research, most commonly used for the measurement of pain. This scale measures the intensity or magnitude of sensations and subjective feelings and the relative strength of attitudes and opinions about specific stimuli.[307,308,309]

First Generation Antipsychotics (FGAs)

SGAs were developed in response to problems with FGAs, including lack of efficacy in some patients, lack of improvement in negative symptoms, and troublesome adverse effects, especially EPS and TD.[310] Multiple studies have been performed between the first and second generation agents, but the results are not clear when considering the aggregate of available information. Although the SGAs are commonly associated with superior effectiveness against the negative symptoms of psychotic disorders, most studies have not sought to prove that point. Of the studies meeting the inclusion criteria for this review, clozapine (Clozaril) and oral ziprasidone (Geodon) do have data that show increased effectiveness in negative symptoms compared to chlorpromazine and haloperidol.[311,312,313] Results from trials that evaluated oral olanzapine (Zyprexa) and risperidone (Risperdal) do not give results consistent with this claim.[314,315,316,317] In general, there is inconclusive evidence that the overall effectiveness of SGAs is better than that for first generation agents in terms of meeting primary outcomes of changes in rating scale scores. However, it is well documented that SGAs are associated with less EPS than first generation antipsychotics.[318,319,320,321,322,323,324,325,326,327,328,329] While that is a distinct advantage, there is the question of long-term adverse events (such as metabolic disorders) linked to SGA use. To that end, there is also the question of long-term effectiveness with these agents. Most studies are under 12 weeks in duration, which is not the optimal study timeframe for measuring therapies for a lifelong illness. Of the agents with long-term data available, a study of clozapine and chlorpromazine over 12 months showed no difference in effectiveness.[330] Risperidone showed continued effectiveness over 3 and 12 months in 2 different studies using haloperidol as a comparator.[331,332] For olanzapine, 2 studies with haloperidol at least 1 year in duration showed mixed results.[333,334] The follow-up rates for studies in patients with these mental health disorders are usually poor. This is easily illustrated by the CATIE study, which had a follow-up rate of 26% over the course of 18 months in Phase 1. All of these issues cloud the issue of the presence of a detectable difference between first and SGAs.

loxapine inhalation powder (Adasuve) and placebo

The efficacy of loxapine inhalation powder in the acute treatment of agitation associated with schizophrenia (n=344) or bipolar I disorder (n=314) was established in 2 short-term (24 hour) randomized, double-blind, placebo-controlled, fixed-dose trials.[335] The primary efficacy endpoint was change from baseline in the PEC score 2 hours after dosing. The key secondary endpoint was the CGI-I score at 2 hours. Inhaled loxapine significantly reduced agitation compared with placebo as assessed by primary and key secondary endpoints. This was apparent 10 minutes following dosing. Using the least squares mean, the change from baseline was -5.8 for placebo versus -8.7 for inhaled loxapine ($p \leq 0.0001$) for the schizophrenia study and -4.7 for placebo versus -9.2 for inhaled loxapine ($p \leq 0.0001$) for the bipolar study.

Second Generation Antipsychotics

aripiprazole (Abilify) and risperidone (Risperdal)

In a 4-week, double-blind study, 404 patients with schizophrenia or schizoaffective disorder were randomized to oral aripiprazole 20 mg daily, aripiprazole 30 mg daily, risperidone 6 mg daily, or placebo.[336] Efficacy assessments included the PANSS and CGI score. Safety and tolerability evaluations included the incidence of EPS, effects on weight, prolactin levels, and QT interval. Aripiprazole and risperidone were better than placebo on all efficacy measures. Separation from placebo occurred at week 1 for PANSS total and positive scores with aripiprazole and risperidone, and for PANSS negative scores with aripiprazole. There were no significant differences between aripiprazole and placebo in mean change from baseline in the EPS rating scales. Mean prolactin levels decreased with aripiprazole but increased 5-fold with risperidone. Mean change in QT interval did not differ significantly from placebo with any active treatment group. Aripiprazole and risperidone groups showed a similarly low incidence of clinically significant weight gain.

aripiprazole (Abilify), quetiapine (Seroquel), and risperidone (Risperdal)

In a multicenter, double-blind, 16-week, placebo-controlled study, 323 patients with chronic, stable schizophrenia or schizoaffective disorder were randomly assigned to receive aripiprazole 2-15 mg daily or placebo in addition to a stable regimen of quetiapine 400-800 mg daily or risperidone 4-8 mg daily.[337] The primary outcome measure was the mean change from baseline to endpoint in the PANSS total score. Nearly 70% of subjects in each arm completed the trial. Adjunctive aripiprazole and placebo groups were similar in the mean change from baseline to endpoint in the PANSS total score (aripiprazole, -8.8; placebo, -8.9; p=0.942). The incidence of treatment-emergent adverse events was similar between groups.

asenapine (Saphris) and olanzapine (Zyprexa)

Two randomized, double-blind, 26-week core studies were conducted in Eastern (EH) and Western Hemisphere (WH) countries and tested the hypothesis that asenapine is superior to olanzapine for persistent negative symptoms of schizophrenia; 26-week extension studies assessed the comparative long term efficacy and safety of these agents.[338] In the core studies, 949 people were randomized to asenapine (n=241 and 244) or olanzapine (n=240 and 224) while there were 134 and 86 asenapine participants and 172 and 110 olanzapine participants in the EH and WH extensions, respectively. The 16-item NSA-16 total score was the primary efficacy variable used to assess negative symptoms. Asenapine was not superior to olanzapine in change in the NSA-16 total score in either core study (EH: p=0.79; WH: p=0.72). Asenapine was superior to olanzapine at week 52 in the WH extension study; however, these positive results need to be interpreted in view of the fact that only a relatively small subset of participants continued in the extension study. Incidence of treatment-emergent adverse events was comparable between treatments across studies. Weight gain was consistently lower with asenapine. Extrapyramidal symptoms were higher with asenapine compared to olanzapine but abbreviated total score changes did not significantly differ between treatments. In conclusion, asenapine superiority over olanzapine for treatment of persistent negative symptoms was not observed in these studies. Both treatments improved persistent negative symptoms, but discontinuation rates were higher with asenapine. This study was funded both by Merck, the manufacturer of asenapine, and Pfizer.

brexpiprazole (Rexulti) and placebo

Two 6-week, randomized, double-blind, placebo-controlled, fixed-dose trials were performed in adult patients to assess the efficacy of brexpiprazole in the treatment of schizophrenia.[339] Patients were required to meet the DSM-IV-TR criteria for schizophrenia. Study 3 and Study 4 patients were randomized to 2 mg or 4 mg once daily of brexpiprazole or placebo. Patients in the treatment group were started at 1 mg once daily on day 1 through day 4 then increased to 2 mg daily on day 5 through day 7. The dose was then maintained at 2 mg once daily or increased to 4 mg once daily for the remaining 5 weeks. The primary endpoint of both trials was the change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total score which is a 30-item scale that rates each item on a scale of 1 (absent) to 7 (extreme). The total PANSS scores can range from 30 (best) to 210 (worst). In Study 3, both the 2 mg daily and 4 mg daily were superior to placebo on the PANSS total score (least-squares mean change from baseline, standard error, of -19.7 to -20.7 versus -12.0, respectively, 95% CI). In Study 4, the 4 mg per day was superior to placebo in the PANSS total score (least-squares mean change from baseline, standard error, of -20 versus -13.5, respectively, 95% CI).

clozapine and olanzapine (Zyprexa)

A randomized, double-blind, parallel study compared treatment with either clozapine (100 to 500 mg/day) or oral olanzapine (5 to 25 mg/day) in 147 patients with schizophrenia, who were either nonresponsive or intolerant of standard antipsychotic therapy.[340] At the 18-week endpoint, no statistically significant differences were found among olanzapine and clozapine based on the efficacy measures used, PANSS and CGI-S. Response rates were not significantly different between olanzapine-treated patients (58%) and clozapine-treated patients (61%). There were no significant differences in either group in regards to occurrences of EPS, and no clinically or statistically significant changes observed in vital signs, electrocardiograms, or laboratory measures. Both treatments were well tolerated.

One hundred fourteen patients with schizophrenia were randomized to clozapine (100 to 400 mg/day) or oral olanzapine (5 to 25 mg/day) for 26 weeks.[341] The double-blind, multicenter trial evaluated the effects of each drug on subjective (SWN, MLDL) and clinical (PANSS and CGI-S) outcomes. The SWN scores improved significantly in both groups. Olanzapine (mean dose 16.2 mg/day) was not inferior to clozapine (mean dose 209 mg/day; group difference 3.2 points in favor of olanzapine; 95% CI, 4.2 to 10.5). MLDL, PANSS, and CGI-S scores improved similarly in each group.

clozapine, olanzapine (Zyprexa), risperidone (Risperdal), and haloperidol

Investigators examined the effects of clozapine, olanzapine, risperidone, and haloperidol on 16 measures of neurocognitive functioning in a double-blind, 14-week trial involving 101 patients with schizophrenia or schizoaffective disorder.[342] Post-hoc analysis showed that global neurocognitive function improved significantly and similarly with olanzapine and risperidone treatment. Clozapine and haloperidol did not significantly improve global scores from baseline, although the effect of clozapine was not significantly different from the other treatment groups. Haloperidol did not significantly improve any of the 4 neurocognitive domains measured: general, executive, and perceptual organization; declarative verbal learning and memory; processing speed and attention; and simple motor functioning. Processing speed and attention was significantly improved to a similar degree by all 3 SGAs. Olanzapine and risperidone demonstrated the greatest improvement in general executive and perceptual organization, declarative verbal learning, and memory. Patients treated with risperidone,

but not olanzapine, exhibited improvement in memory that was superior to that of both clozapine and haloperidol.

iloperidone (Fanapt) and placebo

This trial has been included due to the lack of applicable studies on iloperidone.[343] It evaluated the efficacy and safety of iloperidone in patients with acute exacerbations of schizophrenia. This randomized, placebo-controlled, multicenter study comprised of a 1-week titration period and a 3-week double-blind maintenance period. Patients (n=593) were randomized to iloperidone 24 mg, ziprasidone 160 mg as an active control, or placebo daily. The primary efficacy variable was change from baseline in the PANSS score. Iloperidone demonstrated significant reduction versus placebo on the PANSS score ($p<0.01$). Significant improvement versus placebo was also demonstrated with ziprasidone ($p<0.05$). Compared with ziprasidone, iloperidone was associated with lower rates of sedation, somnolence, extrapyramidal symptoms, akathisia, agitation, and restlessness; iloperidone was associated with higher rates of weight gain, tachycardia, orthostatic hypotension, dizziness, and nasal congestion. A similar amount of QT prolongation was observed with both active treatments, although no patient had a corrected QT interval of 500 msec or greater.

lurasidone (Latuda) and quetiapine XR (Seroquel XR)

The relapse prevention efficacy of lurasidone versus quetiapine XR was evaluated for 12 months in adult patients (n=353) with chronic schizophrenia.[344] Study participants were first required to complete a 6-week placebo-controlled trial with treatment on lurasidone or quetiapine XR. Using a Kaplan-Meier analysis, it was determined that the probability of relapse for participants on lurasidone was 23.7% and 33.6% for quetiapine XR participants. The hazard ratio (95% CI) for probability of relapse was 0.728 (0.41, 1.295; log-rank p=0.28).The probability of hospitalization was estimated to be lower for the lurasidone group versus quetiapine XR (9.8% versus 23.1%; p=0.049). Lurasidone was also shown to be noninferior to quetiapine XR. The study did not measure lurasidone being more effective than quetiapine XR. Since discontinuation due to adverse events was similar between the 2 treatment groups (6.6% for lurasidone versus 4.7% for quetiapine XR), it was concluded that the relapse risk was not due to a difference in tolerability. Maintenance treatment with lurasidone was not associated with any significant effects on weight or metabolic parameters. This study was funded by the manufacturer of lurasidone.

lurasidone (Latuda) and risperidone (Risperdal)

A randomized, double-blind, active-controlled long-term safety and tolerability study of lurasidone was conducted for 12 months in the treatment of schizophrenia.[345] A total of 427 clinically stable outpatients with schizophrenia were randomized to treatment with lurasidone 40-120 mg once daily, and 202 with 2-6 mg of risperidone (active control). Outcome measures included adverse events, vital signs, electrocardiogram (ECG), and laboratory tests. Secondary assessments included efficacy measures of psychopathology using PANSS and CGI-S scores. The 3 most frequent adverse events in the lurasidone group were nausea, insomnia, and sedation. The 3 most frequent adverse events in the risperidone group were increased weight, somnolence, and headache. The median endpoint change in prolactin was significantly higher for risperidone ($p<0.001$). A comparable improvement in efficacy measures was observed with both agents and the rates of relapse were similar. All-cause discontinuation rates were higher for lurasidone versus risperidone. This study was funded by the manufacturer of lurasidone.

lurasidone (Latuda), olanzapine (Zyprexa) and placebo

A 6-week randomized, parallel-group, multicenter control trial evaluated the efficacy of once daily lurasidone (40 mg and 120 mg) versus placebo with the active comparator olanzapine (15 mg/day).[346] Primary efficacy of lurasidone was measured by improvement in the PANSS total score, and CGI-S as a secondary outcome measure. The study enrolled 478 patients diagnosed with schizophrenia for at least 1 year, and hospitalized less than 2 times for acute psychosis. The intent to treat primary efficacy analysis consisted of all patients that received at least 1 study dose, had a baseline and at least 1 post-baseline PANSS assessment. Both doses of lurasidone (along with the active comparator) showed significant improvement on the PANSS total score, PANSS positive and negative subscale score, and CGI-S versus placebo. At the end of week 6, both lurasidone doses, 40 mg and 120 mg, had significantly reduced PANSS scores compared to placebo (-25.7; adjusted p=0.002, and -23.6; adjusted p=0.022 respectively). The active comparator resulted in significantly greater reductions (-28.7, p<0.001). There were no apparent dose-response relationship identified between the lurasidone doses, but the adverse effects and rate of discontinuation in the 120 mg group were higher than the 40 mg group. This study also suggests there is minimal risk of causing adverse outcomes for weight and metabolic effects for lurasidone. When compared to placebo, there were no statistically significant differences between total cholesterol, LDL, HDL, triglycerides, insulin, glucose, HbA1c, or weight. Alternatively, there were significant changes in those measures in the olanzapine active control group.

olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), and ziprasidone (Geodon)

In phase 1 of the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study, an NIMH-funded, double-blind study, 1,493 patients with schizophrenia were randomized to receive oral olanzapine (7.5 to 30 mg/day; mean dose 20.1 mg/day), quetiapine (200 to 800 mg/day; mean dose 543.4 mg/day), risperidone (1.5 to 6 mg/day; mean dose 3.9 mg/day), ziprasidone (40 to 160 mg/day; mean dose 112.8 mg/day) or the FGA, perphenazine (8 to 32 mg/day; mean dose 20.8 mg/day) for up to 18 months.[347] In the multicenter study, 74% of patients discontinued the study medication before 18 months. The time to discontinuation was significantly longer in the olanzapine group (9.2 months) than in the quetiapine (4.6 months; p<0.001) or risperidone (4.8 months; p=0.002) groups. No other comparisons between drugs regarding discontinuation were statistically significant. The PANSS and CGI improved similarly in all treatment groups. Time to discontinuation due to lack of efficacy was longer in the olanzapine group than in the perphenazine (p<0.001), quetiapine (p<0.001), or risperidone (p<0.001) groups. There was no significant difference between groups in time to discontinuation due to intolerable adverse effects. The duration of successful treatment was longer in the olanzapine group than in the quetiapine (p<0.001), risperidone (p=0.002), or perphenazine (p=0.013) groups, but not the ziprasidone group. The duration of successful treatment was longer in the risperidone group than the quetiapine group (p=0.021). No other between-group comparisons were statistically significant. The risk of hospitalization for exacerbation of schizophrenia (normalized for total patient-years of exposure) ranged from 0.29 for olanzapine to 0.66 for quetiapine. The rates of treatment discontinuation due to intolerability ranged from 10% for risperidone to 18% for olanzapine. A subsequent analysis evaluated the extent to which continuing to take the same antipsychotic that a patient had been on prior to the study, rather than switching to a new agent upon entry into the study, affected the time to discontinuation.[348] Results from the analysis indicate that rates of treatment discontinuation were lower for patients that continued their previous therapy than for those that changed their antipsychotic. Removal of data from patients continuing therapy attenuated the original study results, although the original pattern of these results remained the same.

Psychosocial functioning was assessed in the CATIE trial using the Quality of Life Scale.[349] Psychosocial functioning modestly improved for the one-third of phase 1 patients who reached the primary Quality of Life Scale analysis endpoint of 12 months (average effect size 0.19 SD units). For several individual drugs, there were significant changes from baseline, but, overall, there were no significant differences among the agents. Results were similar at 6, 12, and 18 months.

In an effort to compare neurocognitive effects of several SGAs and a FGA, perphenazine, a randomized, double-blind study of patients with schizophrenia was conducted.[350] These patients were assigned to receive treatment with oral olanzapine, perphenazine, quetiapine, or risperidone for up to 18 months. This also included ziprasidone after its FDA approval, as reported previously in the CATIE study. From a cohort of 1,460 patients in the treatment study, 817 patients completed the neurocognitive testing immediately prior to randomization and after 2 months of treatment. The primary outcome was change in neurocognitive composite score after 2 months of treatment. Secondary outcomes included neurocognitive composite score change at 6 months and 18 months after continued treatment and changes in neurocognitive domain. At 2 months, treatment resulted in small neurocognitive improvements of $z=0.13$ ($p<0.002$) for olanzapine, $z=0.25$ ($p<0.001$) for perphenazine, $z=0.18$ ($p<0.001$) for quetiapine, $z=0.26$ ($p<0.001$) for risperidone, and $z=0.12$ ($p<0.06$) for ziprasidone with no significant differences between groups. These results differ from the majority of previous studies and may be due to such factors as more than twice the number of patients in the CATIE trial; lower relative doses of the FGA, perphenazine, used in the CATIE trial; and the broad inclusion and minimal exclusion criteria in the CATIE trial, such as inclusion of patients with comorbid conditions on concomitant medications and/or with current substance abuse. Results at 6 months were similar. After 18 months of treatment, neurocognitive improvement was greater in the perphenazine group than in the olanzapine and risperidone groups. Neurocognitive improvement predicted longer time to treatment discontinuation, independent from symptom improvement, in patients treated with quetiapine or ziprasidone.

Subjects with schizophrenia who had discontinued the SGA randomly assigned during phase 1 of the CATIE investigation were randomly reassigned to double-blind treatment with a different antipsychotic (oral olanzapine 7.5 to 30 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6 mg/day or ziprasidone 40 to 160 mg/day).[351] In the 444-patient study, the time to treatment discontinuation, the primary endpoint, was longer for patients treated with risperidone (7 months; 95% CI, 4.1 to 10 months) and olanzapine (6.3 months; 95% CI, 3.5 to 9.7 months) than with quetiapine (4 months; 95% CI, 3.1 to 4.8 months) and ziprasidone (2.8 months; 95% CI, 2.4 to 4.4 months). Among the 184 patients who discontinued their previous antipsychotic because of inefficacy, olanzapine was more effective than quetiapine and ziprasidone and risperidone was more effective than quetiapine. There were no significant differences between antipsychotics among the 168 patients who discontinued their previous treatment because of intolerability.

Subjects with schizophrenia (n=114) who had been randomly assigned to and then discontinued perphenazine in phase 1 of the CATIE study were reassigned randomly to double-blinded treatment with oral olanzapine (n=38), quetiapine (n=38), or risperidone (n=38).[352] The primary goal was to determine whether there were differences among these 3 treatments in effectiveness, as measured by time to discontinuation for any reason. Secondary outcomes included reasons for treatment discontinuation and measures of drug tolerability. The time to treatment discontinuation was longer for patients treated with quetiapine and olanzapine than with risperidone. No significant differences existed between treatments related to discontinuation due to inefficacy, intolerability, or patient decision.

Phase 4 of the CATIE study compared the response to antipsychotic treatment between patients with and without tardive dyskinesia (TD) and examined the course of TD.[353] This analysis compared 200 patients with DSM-IV-defined schizophrenia and TD and 997 patients without TD, all of whom were randomly assigned to receive 1 of 4 second-generation antipsychotics as used in previous phases (olanzapine, quetiapine, risperidone and ziprasidone). The primary clinical outcome measure was time to all-cause treatment discontinuation, and the primary measure for evaluating the course of TD was change from baseline in Abnormal Involuntary Movement Scale (AIMS) score. Kaplan-Meier survival analysis and Cox proportional hazards regression models were used to compare treatment discontinuation between groups. Changes in Positive and Negative Syndrome Scale (PANSS) and neurocognitive scores were compared using mixed models and analysis of variance. Treatment differences between drugs in AIMS scores and all-cause discontinuation were examined for those with TD at baseline. Percentages of patients meeting criteria for TD post-baseline or showing changes in AIMS scores were evaluated with chi square tests. Time to treatment discontinuation for any cause was not significantly different between the TD and non-TD groups (chi square(1) = 0.11, p=0.743). Changes in PANSS scores were not significantly different (p=0.366), but patients with TD showed less improvement in neurocognitive scores (p=0.011). Among patients with TD, there were no significant differences between drugs in the decline in AIMS scores (p=0.811); 55% met criteria for TD at 2 consecutive visits post-baseline, 76% met criteria for TD at some or all post-baseline visits, 24% did not meet criteria for TD at any subsequent visit, 32% showed 50% or greater decrease in AIMS score, and 7% showed a 50% or greater increase in AIMS score. The authors concluded patients with schizophrenia with and without TD were similar in time to discontinuation of treatment for any cause and improvement in psychopathology, but differed in neurocognitive response. There were no significant differences between treatments in the course of TD, with most patients showing either persistence of or fluctuation in observable symptoms.

olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), and clozapine

The CATIE investigation was continued in order to compare clozapine to other SGAs in patients who had discontinued the newer agents during phase 1 CATIE study.[354] Phase 2 of the study consisted of 99 patients who had inadequate response to treatment with oral olanzapine, quetiapine, risperidone, or ziprasidone during phase 1 or 1b. Patients were randomly assigned to open-label treatment with clozapine (n=49) or blinded treatment with another newer SGA not previously administered in the trial (olanzapine [n=19], quetiapine [n=15], or risperidone [n=16]). Results indicated that time until treatment discontinuation for any reason was longer for clozapine (median=10.5 months; 95% CI, 7.3 to 16.1 months) than for quetiapine (median=3.3 months; 95% CI, 1 to 4.9 months), risperidone (median=2.8 months; 95% CI, 1.1 to 4 months), or olanzapine (median=2.7 months; 95% CI, 1.9 to 11.9 months). Time to discontinuation because of inadequate therapeutic effect was longer for clozapine (median 13.7 months) than for olanzapine, quetiapine, or risperidone. At 3-month assessments, PANSS total scores had decreased more in patients treated with clozapine than in patients treated with quetiapine or risperidone, but not olanzapine. Treatment discontinuations in 2 patients treated with clozapine occurred with the development of agranulocytosis and eosinophilia. Clozapine demonstrated responsiveness in patients who had failed other SGAs, but its use requires safety monitoring for blood dyscrasias.

aripiprazole (Abilify), ziprasidone (Geodon), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), clozapine, perphenazine, and long-acting injectable fluphenazine decanoate

Phase 3 of the CATIE trial conducted an examination in 270 patients to investigate the efficacy and safety of 9 antipsychotic regimens in patients with schizophrenia, who had discontinued their antipsychotic treatment in phases 1 and 2 of the study.[355] Open-label treatment options were monotherapy with oral aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, long-acting injectable fluphenazine decanoate, or a combination of any 2 of these treatments. The distribution of patients in each treatment option was similar (range 33-41), except very few patients selected fluphenazine decanoate or perphenazine (n=9, n=4, respectively). Results indicated that the remaining 7 antipsychotic treatments demonstrated similar efficacy, and patients who had mild symptom severity prior to entering the study demonstrated the most modest improvement; however, patients taking clozapine and combination antipsychotic treatment were the most symptomatic. Patients taking aripiprazole or ziprasidone had the highest BMI, and adverse effects varied among the treatments, but discontinuation due to intolerability were rare (7%).

olanzapine (Zyprexa) and risperidone (Risperdal)

An international, multicenter, double-blind, parallel-group, 28-week prospective study was conducted with 339 patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder.[356] The study indicated that both oral olanzapine and risperidone were safe and effective in the management of psychotic symptoms. However, olanzapine demonstrated greater efficacy in negative symptoms and overall response rate ($\geq$40% decrease in the PANSS total score). A greater proportion of the olanzapine-treated than risperidone-treated patients maintained response at 28 weeks based on Kaplan-Meier survival curves. The incidences of extrapyramidal side effects, hyperprolactinemia, and sexual dysfunction were lower in olanzapine-treated than risperidone-treated patients. In addition, fewer adverse events were reported by olanzapine-treated patients than by their risperidone-treated counterparts. This study was performed by the manufacturer of olanzapine.

In a multicenter, double-blind study, 150 patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder were randomized to oral olanzapine 10 to 20 mg/day (mean dose 17.7 mg/day) or risperidone 4 to 12 mg/day (mean dose 7.9 mg/day) for a maximum of 28 weeks.[357] Response, defined as a 40% improvement in PANSS, was more likely to be maintained with olanzapine than with risperidone (p=0.048). A smaller proportion of olanzapine-treated patients required anticholinergic therapy compared with risperidone-treated patients (25.3 versus 45.3%; p=0.016).

In a double-blind study, 377 patients with schizophrenia or schizoaffective disorder were randomly assigned to receive risperidone (mean dose 4.8 mg/day) or olanzapine (mean dose 12.4 mg/day) for 8 weeks.[358,359] Total PANSS scores, as well as PANSS negative and positive subscales, were improved in both groups; comparison of individual factors found no significant differences at endpoint. Cognitive function, assessed with a focused cognitive assessment battery, showed no differences in the effects of the 2 drugs. Correcting for the effects of anticholinergic treatment did not alter the magnitude of cognitive effects, indicating that these agents have a direct effect on cognitive deficits in schizophrenia. Seventy-five percent of the participants completed the trial with no between-treatment differences in the proportion of dropouts. Similar proportions of the risperidone and olanzapine groups reported EPS (24 and 20%, respectively). Severity of EPS was low in both groups with no between-group differences. An increase in body weight of at least 7% was seen in 27% of olanzapine participants and 12% of risperidone participants.

olanzapine (Zyprexa) and ziprasidone (Geodon)

In a multicenter, double-blind, parallel-group, 28-week study, 548 patients with schizophrenia were randomly assigned to treatment with oral olanzapine (10 to 20 mg/day) or ziprasidone (80 to 160 mg/day).[360] The study was completed by more olanzapine-treated patients (59.6%) than ziprasidone-treated patients (42.4%; p<0.05). At 28 weeks, the olanzapine-treated patients showed more improvement than the ziprasidone-treated patients on the PANSS (the primary efficacy measure) and all subscales and on the CGI-I and CGI-S. The responder rate was higher for olanzapine than for ziprasidone. Extrapyramidal symptoms were not significantly different between groups. There was a notable difference between the 2 drugs on the effect on weight with the olanzapine group increasing by a mean 3.1 kg, and the ziprasidone group decreasing by a mean 1.1 kg. Fasting lipid profiles were better in the ziprasidone group; there was no significant difference in fasting glucose level. This study was conducted by the manufacturer of olanzapine.

An 8-week, double-blind, parallel-group, randomized, controlled multicenter trial of 76 patients with schizophreniform disorder, schizophrenia or schizoaffective disorder (diagnosis less than 5 years), and a maximum lifetime antipsychotic treatment of less than 16 weeks participated in the study to compare the efficacy and tolerability of ziprasidone (80 to 160 mg daily) and olanzapine (10 to 20 mg daily) in patients with recent-onset schizophrenia.[361] Efficacy of ziprasidone and olanzapine was measured using the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression (CGI) Scale, the Calgary Depression Scale for Schizophrenia (CDSS), and the Heinrich Quality of Life Scale (HQLS). Tolerability assessments included laboratory assessments, body weight, and electroencephalogram. Olanzapine (n=34) and ziprasidone (n=39) showed equal efficacy as measured by the various scales; however, mean weight gain was significantly higher in the olanzapine group (6.8 versus 0.1 kg, p<0.001). Ziprasidone was associated with decreasing levels of triglycerides, cholesterol, and transaminases, while these parameters increased in the olanzapine group (all p values <0.05). There were no significant differences in fasting glucose and prolactin levels or in cardiac or sexual side effects. Patients on ziprasidone used biperiden for extrapyramidal side effects more frequently (p <0.05). The results of this study indicate that ziprasidone and olanzapine have comparable therapeutic efficacy but differ in their side effect profile. However, there is a risk of a type II error with this sample size. Clinically significant weight gain and laboratory abnormalities appear early after initiating treatment and are more prominent with olanzapine, while more patients on ziprasidone received anticholinergic drugs to treat extrapyramidal symptoms. This study was sponsored by the manufacturer of ziprasidone.

paliperidone ER (Invega) and olanzapine (Zyprexa)

In a double-blind study, 630 patients with schizophrenia were randomized to receive paliperidone ER 6 mg, 9 mg, or 12 mg, olanzapine 10 mg, or placebo once daily for 6 weeks.[362] The primary endpoint was change in total PANSS score from baseline; investigators did not include olanzapine in the efficacy analysis. Improvement in mean total PANSS scores was significantly greater with paliperidone ER than placebo at all time points starting at day 4 for the 12 mg dosage (p<0.01) and day 8 for the lower doses (p<0.05). Response rates (≥30% reduction in total PANSS) were higher with all paliperidone ER doses (51 to 61%) than placebo (30%; p<0.001). The percentage of patients completing this study was approximately 20 to 30% higher in the active treatment groups, primarily due to a higher rate of discontinuation in the placebo group experiencing lack of efficacy.

In a similar study, 630 patients with schizophrenia were randomized to receive paliperidone ER 3 mg, 9 mg, 15 mg, oral olanzapine 10 mg, or placebo once daily.[363] Significant improvement ($p \leq 0.003$) in PANSS total scores were noted with all doses of paliperidone ER from day 4 forward. Response rates ($\geq$30% reduction in total PANSS scores) occurred in a dose-related fashion in 40 to 53% of patients receiving paliperidone ER compared to 18% of patients receiving placebo ($p \leq 0.001$). Response rates were 52% for olanzapine.

In a third study of similar design, 444 patients with schizophrenia were randomized to receive fixed daily doses of paliperidone ER 6 mg or 12 mg, olanzapine 10 mg, or placebo for 6 weeks.[364] In the study, significant improvement, compared to placebo, was noted from day 4 forward for the lower dose of paliperidone ER and from day 15 forward for the higher dose of paliperidone ER. Clinical response (as defined in the previous studies) was significantly more common in the paliperidone ER groups (50 to 51%) than in the placebo group (34%; $p \leq 0.025$); the response rate in the olanzapine group was 46%.

quetiapine (Seroquel) and risperidone (Risperdal)

In a double-blind study, 673 patients with schizophrenia were randomized to receive quetiapine 200 to 800 mg/day (mean dose 525 mg/day) or risperidone 2 to 8 mg/day (mean dose 5.2 mg/day) for 8 weeks.[365] At the conclusion of the study, there were no significant differences between groups in PANSS total scores, response rates, or CGI. There was a significantly greater improvement in the PANSS positive subscale in the risperidone group ($p=0.03$). The rate of EPS was higher with risperidone (22%) than with quetiapine (13%; $p<0.01$). Somnolence was more common with quetiapine (25%) than with risperidone (20%; $p=0.04$). Prolactin levels increased with risperidone and decreased with quetiapine ($p<0.001$ for comparison of change in prolactin levels). This study was performed by the manufacturer of quetiapine.

quetiapine (Seroquel) and quetiapine XR (Seroquel XR)

A double-blind, double-dummy study was conducted to evaluate the efficacy and safety of switching patients with clinically stable schizophrenia from twice daily quetiapine immediate-release (IR) to the same dose of quetiapine once daily extended release (XR).[366] All patients initially received quetiapine IR 400–800 mg twice daily for 4 weeks and were then randomized to once daily equivalent dose of quetiapine XR or maintained on quetiapine IR for 6 weeks. The primary efficacy variable was the proportion of patients who discontinued treatment due to lack of efficacy or who had at least a 20% increase in their positive or negative symptom scale scores. In total, 497 patients were randomized to either the XR formulation (n=331) or the IR formulation (n=166). Non-inferiority was not demonstrated for the modified intention to treat population; however, non-inferiority was demonstrated for the per-protocol population (XR=5.3%, IR=6.2%, $p=0.0017$). No serious adverse effects were demonstrated for either of the formulations. The authors concluded that efficacy was maintained without compromising safety and/or tolerability when switching patients with stable schizophrenia from the twice daily IR formulation to the once daily XR formulation of quetiapine.

risperidone (Risperdal) and ziprasidone (Geodon)

Patients with an acute exacerbation of schizophrenia or schizoaffective disorder were randomly assigned in a double-blind fashion to oral ziprasidone 40 to 80 mg twice daily or risperidone 3 to 5 mg twice daily for 8 weeks.[367] Primary efficacy measures were PANSS total score and CGI-S score. In the 296-patient study, equivalence was demonstrated in the 2 primary efficacy measurements, PANSS and CGI-S, as well as in PANSS negative subscale scores, BPRS, PANSS total, and CGI-I responder rates. Both agents were well tolerated. Risperidone exhibited significantly greater movement disorder burden ($p<0.05$), higher incidences of prolactin elevation, and clinically relevant weight gain. Study dosing was above current recommendations for some risperidone-treated patients (mean dose 7.4 mg/day) and below current recommendations for some ziprasidone-treated patients (mean dose 114.2 mg/day). Both agents equally improved psychotic symptoms, and both were generally well tolerated. In a 44-week extension study, patients (n=139) continued their current treatment.[368] There were no significant differences in PANSS and CGI-S scores at study endpoint. Ziprasidone patients showed greater MADRS improvement in depressive symptoms compared to risperidone patients ($p<0.05$). Risperidone was associated with more EPS, prolactin, and weight gain adverse events than ziprasidone. The median doses were 120 mg/day for ziprasidone and 8 mg/day for risperidone.

ziprasidone (Geodon) and clozapine (Clozaril)

An 18-week, randomized, double-blind trial evaluated ziprasidone as an alternative to clozapine in treatment-refractory schizophrenia patients.[369] Patients (n=147) had a history of resistance and/or intolerance to at least 3 acute cycles with different antipsychotics given at therapeutic doses, PANSS score $\geq$80, and CGI-S score $\geq$ 4. Patients were randomized to ziprasidone 80-160 mg daily or clozapine 250-600 mg daily. Baseline-to-endpoint decreases in PANSS total scores were similar in the ziprasidone (-25.0, 95% CI, -30.2 to -19.8) and clozapine groups (-24.5, 95% CI, -29.7 to -19.2). A progressive and significant reduction from baseline in PANSS total score was observed from day 11 in both study arms. There were also significant improvements for PANSS subscales, CGI-S, CG-I, CDSS, and GAF without between-drug differences. The 2 treatment groups had similar rates of early discontinuations due to adverse effects, which were of similar severity in the 2 groups. Ziprasidone, but not clozapine, did show a significant reduction of SAS and AIMS scores. Ziprasidone also had a more favorable metabolic profile.

Injectable Antipsychotics

aripiprazole (Abilify Maintena)

Aripiprazole intramuscular (IM) depot was evaluated in a randomized, double-blind, placebo-controlled study for efficacy and tolerability as maintenance treatment in adults meeting DSM-IV-TR schizophrenia criteria.[370] Patients were switched to oral aripiprazole during phase-I (4 to 6 weeks), and then were stabilized on oral aripiprazole 10-30 mg/day during phase-II (4 to 12 weeks). In phase-III, subject who met stability criteria on oral aripiprazole were assigned to single-blind aripiprazole IM depot 400 mg. Oral aripiprazole (10-20 mg/day) was continued for the first 2 weeks of phase-III to maintain therapeutic plasma concentrations. Subjects (n=403) who met stability criteria for aripiprazole IM depot stabilization for 12 consecutive weeks were randomly assigned to aripiprazole IM depot or placebo during a 52-week, double-blind maintenance phase. The primary outcome measure was time to exacerbation of psychotic symptoms/impending relapse (event). Safety and tolerability were also assessed. The study was terminated early because efficacy was demonstrated by the

preplanned interim analysis. Time to impending relapse was significantly delayed with aripiprazole IM depot treatment compared with placebo in both the interim analysis and the final analysis ($p<0.0001$). The hazard ratio at final analysis was 5.03 (95% CI, 3.15-8.02). Improvements in CGI-S and PANSS total scores were maintained with aripiprazole IM depot treatment but showed significant worsening with placebo ($p<0.0001$). The most common treatment-emergent adverse events were insomnia, tremor, and headache.

fluphenazine decanoate and haloperidol decanoate (Haldol Decanoate)

An 8-month, parallel-group, double-blind trial comparing haloperidol decanoate with fluphenazine decanoate in the maintenance treatment schizophrenia was performed in 72 outpatients.[371] The initial injection interval was based on pretrial maintenance treatment with fluphenazine. The dosage equivalency of haloperidol decanoate (75 mg) to fluphenazine decanoate (25 mg) used was 3:1, and injections were given every 2, 3, or 4 weeks. No statistically significant differences in therapeutic effect were found between the drugs. Both drugs had a similar EPS profile.

A 20-week, double-blind study compared the efficacy and safety of haloperidol decanoate and fluphenazine decanoate, both given every 4 weeks, in 51 schizophrenia patients.[372] The mean dose of fluphenazine decanoate was 84 mg compared to 122 mg for the haloperidol decanoate group, suggesting a potency ratio of 1:1.4. Injections were administered every 4 weeks. The CPRS subscale for schizophrenic symptoms and the subscale for depression symptoms each showed a statistically significant improvement ($p<0.05$) for the haloperidol decanoate group after 20 weeks. No significant between-group differences were found in the incidence of EPS at week 20. More patients on fluphenazine decanoate gained weight than patients on haloperidol decanoate, but the difference was not statistically significant.

olanzapine (Zyprexa Relprevv)

Outpatients (n=1,065) with schizophrenia who had been stable on an oral regimen of olanzapine were randomly assigned to 24 weeks of double-blind treatment with olanzapine 150 mg or 300 mg IM every 2 weeks, 45 mg (reference dose), or 405 mg IM every 4 weeks, or their stabilized dose of oral olanzapine.[373] At 24 weeks, 93% of oral olanzapine-treated patients, as well as most olanzapine long-acting injection-treated patients receiving high, medium, low, and very low doses (95, 90, 84, and 69%, respectively), remained exacerbation-free, with the 405 mg 4-week regimen and pooled 2-week regimen (150 mg and 300 mg doses) demonstrating efficacy similar to that of oral olanzapine, as well as to each other. The 3 standard long-acting doses were superior to the reference dose based on time to exacerbation. Incidence of weight gain greater than 7% of baseline was 21% for oral olanzapine compared with 21, 15, 16, and 8 for the olanzapine 405 mg, 300 mg, 150 mg, and 45 mg treatment groups, respectively.

paliperidone palmitate (Invega Sustenna)

The efficacy and safety of injectable paliperidone was measured in adults with schizophrenia.[374] Eligible patients were transitioned from previous antipsychotics to paliperidone during a 9-week, open-label phase. Stable patients continued into the 24-week maintenance phase. At maintenance phase endpoint, stabilized patients were randomized to either continue paliperidone at their stabilized dose (within prescribing information limits) or begin placebo in the double-blind phase. Time-to-relapse (primary endpoint) favored paliperidone ($p<0.0001$) at the interim (n=312) and final analyses (n=408). The hazard ratio at the final analysis was 3.6 (95% CI, 2.45 to 5.28). Across phases, the incidence of glucose-related adverse events was low, while mean weight increased by 1.9 kg for paliperidone and remained unchanged for placebo patients.

paliperidone palmitate (Invega Sustenna) and haloperidol decanoate (Haldol Decanoate)

A randomized, double-blind, multicenter clinical trial was conducted in adult patients (n=311) diagnosed with schizophrenia or schizoaffective disorder who were clinically assessed to be at risk of relapse and likely to benefit from a long-acting injectable antipsychotic.[375] The primary endpoint was to compare the effectiveness of paliperidone palmitate with haloperidol decanoate. There was no statistically significant difference in the rate of efficacy failure for paliperidone palmitate compared with haloperidol decanoate (adjusted HR, 0.98; 95% CI, 0.65 to 1.47). The number of participants who experienced efficacy failure was 49 (33.8%) in the paliperidone palmitate group and 47 (32.4%). The haloperidol decanoate group was associated with more weight gain and greater increases in serum prolactin, whereas haloperidol decanoate was associated with more akathisia.

paliperidone palmitate (Invega Sustenna) and oral antipsychotics

The Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study was a prospective, open-label, randomized, 15-month study conducted between May 5, 2010, and December 9, 2013, comparing long-acting injectable paliperidone palmitate and oral antipsychotic medications in 450 subjects (444 subjects were included in the intent-to-treat population) with schizophrenia (according to DSM-IV criteria).[376] Subjects were randomly assigned to once-monthly paliperidone palmitate injections or daily oral antipsychotics (randomly assigned from 7 acceptable, prespecified oral antipsychotics) for 15 months. The primary endpoint was time to first treatment failure, defined as arrest/incarceration; psychiatric hospitalization; suicide; treatment discontinuation or supplementation due to inadequate efficacy, safety, or tolerability; or increased psychiatric services to prevent hospitalization. Time to first treatment failure was determined by a blinded event-monitoring board and analyzed with the Kaplan-Meier method. Paliperidone palmitate was associated with significant delay in time to first treatment failure versus oral antipsychotics (hazard ratio, 1.43; 95% CI, 1.09 to 1.88; log rank p=0.011). Observed treatment failure rates over 15 months were 39.8% and 53.7%, respectively. Arrest/incarceration and psychiatric hospitalization were the most common reasons for treatment failure in the paliperidone palmitate and oral antipsychotic groups (21.2% versus 29.4% and 8% versus 11.9%, respectively). The 5 most common treatment-emergent adverse events for the paliperidone palmitate treatment group were injection site pain (18.6%), insomnia (16.8%), weight increase (11.9%), akathisia (11.1%), and anxiety (10.6%). Once-monthly paliperidone palmitate demonstrated superiority compared to oral antipsychotics in delaying time to treatment failure.

paliperidone palmitate (Invega Trinza)

A long-term double-blind, placebo-controlled randomized-withdrawal trial was conducted on patients who met DSM-IV-TR criteria for schizophrenia to assess time to relapse.[377] Patients could be enrolled in the study with acute symptoms (if previously treated with oral antipsychotics) or be clinically stable (if treated with long-acting injectable antipsychotics). Those patients who were currently receiving the 39 mg dose of 1 month paliperidone palmitate were ineligible. Three treatment periods included: a 17-week flexible dose open-label stabilization period including a total of 506 patients with 1 month of individualized paliperidone palmitate dosing to achieve a PANSS score of < 70 to demonstrate clinical stability, a 12-week open-label stabilization period including a total of 379 patients to achieve a PANSS score of < 70 and scores of ≤ 4 for 7 specific PANSS items, a variable length double-blind treatment period including a total of 305 stabilized patients randomized to Invega Trinza (same dose as open-label phase) or placebo until relapse, early withdrawal or the end of the study. The primary efficacy variable was time to first relapse and the study ended early due to Invega Trinza demonstrating a statistically significant longer time to relapse than placebo. Relapse events were experienced in 23% patients in the placebo group and in 7.4% of patients in the Invega Trinza arm.

risperidone (Risperdal Consta) and olanzapine (Zyprexa)

To compare risperidone IM and oral olanzapine, 377 patients with schizophrenia were randomized to receive risperidone IM 25 mg or 50 mg every 14 days or oral olanzapine 5-20 mg daily.[378] Over 13 weeks, risperidone IM was at least as effective as oral olanzapine. In the 12-month phase, significant improvements in the PANSS total and factor scores from baseline were seen in both groups of patients. Both treatments were well tolerated. A 2-year observational study of risperidone IM and various oral SGAs concluded that risperidone IM showed greater improvement in treatment retention and clinical symptoms of schizophrenia.[379]

risperidone (Risperdal Consta) and oral antipsychotics

A 3-year, open-label, parallel-group, randomized controlled study of 369 patients with schizophrenia or schizoaffective disorder in the Veterans Affairs (VA) system was conducted to determine if long-acting injectable risperidone improves adherence to treatment and outcomes in schizophrenia.[380] Treatments were not blinded since giving placebo injections to the comparison group would interfere with the goal of comparing the acceptability of 2 different methods of medication administration. However, the endpoints were blindly rated. Patients who met the initial diagnosis criteria, as well as having a hospitalization within the previous 2 years or at imminent risk for hospitalization, were randomized to receive long-acting injectable risperidone 25 to 50 mg every 2 weeks or a psychiatrist's choice of an oral antipsychotic. The primary endpoint was hospitalization in a VA or non-VA psychiatric hospital. Symptoms, quality of life, and functioning were assessed in blinded videoconference interviews. Of 369 participants, 40% were hospitalized at randomization, 55% were hospitalized within the previous 2 years, and 5% were at risk for hospitalization. The rate of hospitalization after randomization was not significantly lower among patients who received long-acting injectable risperidone than among those who received oral antipsychotics (39% after 10.8 months versus 45% after 11.3 months; hazard ratio, 0.87; 95% confidence interval, 0.63 to 1.2). Psychiatric symptoms, quality of life, scores on the Personal and Social Performance scale of global functioning, and neurologic side effects were not significantly improved with long-acting injectable risperidone as compared with control treatments. Patients who received long-acting injectable risperidone reported more adverse events at the injection site and more extrapyramidal symptoms. The authors concluded that long-acting injectable risperidone was not

superior to a psychiatrist's choice of oral treatment in patients with schizophrenia and schizoaffective disorder who were hospitalized or at high risk for hospitalization, and it was associated with more local injection-site and extrapyramidal adverse effects. This study was supported by the VA Cooperative Studies Program and the manufacturer of long-acting injectable risperidone.

ziprasidone (Geodon) and haloperidol decanoate (Haldol Decanoate)

In a 6-week, multicenter, investigator-blinded, parallel-group study, patients with schizophrenia or schizoaffective disorder were randomized to ziprasidone (IM up to 3 days, then oral 40-80 mg twice daily) or haloperidol (IM up to 3 days, then oral 5-20 mg daily).[381] Following IM treatment, patients receiving ziprasidone (n=427) showed significantly improved BPRS total scores compared with those receiving haloperidol (n=138, $p<0.0018$). At endpoint, there were no significant between-group differences in BPRS total scores. There was a significantly greater improvement in BPRS negative subscale scores in ziprasidone patients, both at the end of IM treatment ($p<0.0001$) and at study endpoint ($p<0.0001$). Haloperidol patients exhibited significantly greater increases in EPS at the end of IM treatment and at endpoint ($p<0.0001$).

Bipolar Disorder

Efficacy Scales

CGI-BP (Clinical Global Impression – bipolar depression) – The CGI was modified specifically for use in assessing global illness severity and change in patients with bipolar disorder.[382]

HAM-D (Hamilton Depression Rating Scale) – This scale is used to assess the severity of major depressive disorder (MDD) in patients already diagnosed with an affective disorder. It is the most widely used and accepted outcome measure for evaluating depression severity. The HAM-D is the standard depression outcome measure used in clinical trials presented to the Food and Drug Administration (FDA) by pharmaceutical companies for approval of New Drug Applications. The standard HAM-D-21 contains 21 questions. The more commonly used HAM-D-17 excludes 4 questions relating to diurnal variation, de-personalization and de-realization, paranoid symptoms, and obsessional and compulsive symptoms. The remaining 17 questions are related to symptoms, such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels, and weight loss.[383]

MADRS (Montgomery-Asberg Depression Rating Scale) – This scale measures the effect of treatment on depression severity and, as such, requires a baseline assessment before treatment with subsequent assessments during the course of treatment. The MADRS measures the severity of a number of symptoms, including mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation, and restlessness.[384]

YMRS (Young Mania Rating Scale) – This scale is used to assess disease severity in patients already diagnosed with mania. It is a checklist of 11 manic symptoms that is administered by a trained clinician based on a personal interview.[385] The scale, which follows the style of the HAM-D, was designed to be sensitive to the effects of treatments on manic symptoms.

Bipolar Disorder - Mania

aripiprazole (Abilify) and haloperidol

In a double-blind study, investigators randomized 347 patients with bipolar I disorder experiencing acute manic or mixed episodes to receive either oral aripiprazole 15 mg/day or haloperidol 10 mg/day for 12 weeks.[386] Doses could be increased after week 1 or 2 to aripiprazole 30 mg or haloperidol 15 mg. Average daily dosages at week 12 were aripiprazole 21.6 mg and haloperidol 11.1 mg, respectively. At the conclusion of the study, response (defined as at least a 50% improvement in YMRS) was noted in 50% of patients randomized to aripiprazole and 28% of patients receiving haloperidol ($p<0.001$). These rates were similar to the continuation rates of 51 and 29%, respectively. The study was funded by the manufacturer of aripiprazole.

asenapine (Saphris) and placebo

This trial has been included due to the lack of applicable studies on asenapine.[387] This randomized, double-blind, placebo-controlled trial assessed the efficacy, safety, and tolerability of asenapine in bipolar disorder mania. Adults (n=488) experiencing manic or mixed episodes were randomized to 3 weeks of asenapine 5 or 10 mg twice daily, placebo, or olanzapine 5-20 mg daily. Primary efficacy, YMRS total score change from baseline to day 21, was assessed with last observation carried forward. Mean daily doses were 18.4 mg asenapine and 15.9 mg olanzapine. Least squares mean changes in YMRS total score on day 21 were significantly greater with asenapine than placebo (-11.5 versus -7.8; $p<0.007$), with an advantage seen as early as day 2 (-3.2 versus -1.7; $p=0.022$). Changes with olanzapine on days 2 and 21 also exceeded placebo (both $p<0.0001$). YMRS response and remission rates with olanzapine, but not asenapine, exceeded those of placebo. The incidence of EPS was 10.3, 3.1, and 6.8% with asenapine, placebo, and olanzapine, respectively. The incidence of clinically significant weight gain was 7.2, 1.2, and 19%. A second study by the same authors found similar results, as did their 9-week extension study.[388, 389]

lurasidone (Latuda) and placebo

The efficacy of lurasidone, as monotherapy, was established in a 6-week, double-blind, placebo-controlled, multicenter, study of adults who met DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder.[390] Patients were randomized to receive lurasidone (20-60 mg/day [n=166] or 80-120 mg/day [n=169]) or placebo (n=170) for 6 weeks. The primary and key secondary endpoints were change from baseline to week 6 on the MADRS and depression severity score on the CGI-BP. Lurasidone treatment significantly reduced mean MADRS total scores for both the 20-60 mg/day group and the 80-120 mg/day group by a least-squares mean change of -15.4 for each group compared to placebo which had a least-squares mean change of -10.7. Greater endpoint reduction in CGI-BP depression severity scores were also achieved at -1.8 and -1.7 for the 20-60 mg/day and 80-120 mg/day groups respectively compared to placebo at -1.1. Discontinuation rates due to adverse events were similar between lurasidone and placebo. The most frequent adverse events associated with lurasidone were nausea, headache, akathisia, and somnolence. Minimal changes in weight, lipids, and measures of glycemic control were observed with lurasidone. Similarly, the efficacy of lurasidone as adjunctive therapy with lithium or valproate, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients.[391]

olanzapine (Zyprexa) versus haloperidol

In a double-blind study, 453 patients with bipolar mania were randomized to receive oral olanzapine 5-20 mg/day or haloperidol 3-15 mg/day for 2 successive 6-week periods.[392] Remission rates at week 6, as determined by YMRS ≤12 and HAM-D ≤8, were similar in the olanzapine and haloperidol groups (52 and 46%, respectively; p=0.15). Relapse rates were also similar (13 to 15%) in each group. Worsening of EPS was more common with haloperidol. Weight gain was noted only with olanzapine (2.8 kg; p<0.001 compared to haloperidol). The study was performed by the manufacturer of olanzapine.

quetiapine (Seroquel) and haloperidol

Investigators randomized 302 patients with bipolar mania to receive double-blind treatment with quetiapine up to 800 mg/day, haloperidol up to 8 mg/day, or placebo for 12 weeks.[393] While both active treatments were superior to placebo in improvement in YMRS at day 21, haloperidol was superior to quetiapine also (p<0.05). There was no significant difference between active treatments at any other weekly assessment during the study. Both active treatments maintained their superiority over placebo throughout the study. Response rates at day 84 were higher with quetiapine (61%) and haloperidol (70%) than with placebo (39%; p<0.05); there was no significant difference between active treatments. Withdrawal rates were approximately 54% for each of the active treatments and 42% for placebo (p<0.05). Withdrawal due to adverse events was twice as common with haloperidol as with quetiapine or placebo.

risperidone (Risperdal) and haloperidol

In a double-blind study, 438 patients were randomized to receive risperidone 1-6 mg/day (mean dose 4.2 mg/day), haloperidol 2-12 mg/day (8 mg/day), or placebo for 3 weeks, followed by 1 of the active treatments for an additional 9 weeks for the management of bipolar mania.[394] At week 3 and throughout the remaining 9 weeks, mean YMRS reductions from baseline were greater in patients receiving either active treatment than those receiving placebo. There was no significant difference between risperidone and haloperidol. EPS occurred more often in the haloperidol group than in the risperidone or placebo groups.

ziprasidone (Geodon)

To evaluate the efficacy and safety of ziprasidone adjunctive to a mood stabilizer for the maintenance treatment of bipolar mania, 240 patients with bipolar I disorder with a Mania Rating Scale score ≥14 were studied.[395] Subjects achieving ≥ 8 consecutive weeks of stability with open-label ziprasidone (80-160 mg daily) and lithium or valproate were randomly assigned in the 6-month, double-blind maintenance period to ziprasidone plus mood stabilizer or placebo plus mood stabilizer. The primary and key secondary endpoints were the time to intervention for a mood episode and time to discontinuation for any reason, respectively. Intervention for a mood episode was required in 19.7 and 32.4% of ziprasidone and placebo subjects, respectively. The time to intervention for a mood episode was significantly longer for ziprasidone than placebo (p=0.0104). The median time to intervention for a mood episode among those requiring such an intervention was 43 days for ziprasidone versus 26.5 days for placebo. The time to discontinuation for any reason was significantly longer for ziprasidone (p=0.0047). Adjunctive ziprasidone treatment was well tolerated.

Bipolar Disorder - Depression

olanzapine (Zyprexa) and olanzapine / fluoxetine (Symbyax)

An 8-week clinical trial in 833 adults with depression associated with bipolar I disorder found the olanzapine/fluoxetine combination (doses of 6/25 mg, 6/50 mg, or 12/50 mg per day) was more effective than oral olanzapine alone (5 to 20 mg/day) or placebo.[396] At week 8, MADRS remission criteria were met by 25% of the placebo group, 33% of the olanzapine group, and 49% of olanzapine/fluoxetine group. Treatment-emergent mania did not differ among groups (placebo 6.7%, olanzapine 5.7%, and olanzapine/fluoxetine 6.4%). Adverse events for olanzapine/fluoxetine therapy were similar to those for olanzapine therapy but also included higher rates of nausea and diarrhea. A secondary analysis was completed to determine the benefits of olanzapine alone and olanzapine/fluoxetine for improving HRQOL using both a generic and a depression-specific HRQOL instrument.[397] Based on the analyses, patients with bipolar depression receiving olanzapine or olanzapine/fluoxetine for 8 weeks had greater improvement in HRQOL than those receiving placebo. Treatment with olanzapine/fluoxetine was associated with greater improvement in HRQOL than olanzapine alone.

quetiapine ER (Seroquel XR)

To evaluate the effectiveness of quetiapine ER once daily in bipolar depression, this double-blind, placebo-controlled study was performed in acutely depressed adults with bipolar I or II disorder.[398] Patients were randomized to 8 weeks of quetiapine ER 300 mg daily or placebo. The primary outcome measure was change from baseline to week 8 in MADRS total score. Quetiapine ER (n=133) showed significantly greater improvement in depressive symptoms compared with placebo (n=137) from week 1 ($p<0.001$) through week 8 ($p<0.001$). Mean change in MADRS total score at week 8 was -17.4 in the quetiapine ER group and -11.9 in the placebo group ($p<0.001$). Response ($\geq$50 reduction in MADRS total score) and remission (MADRS total score$\leq$12) rates at week 8 were significantly higher with quetiapine ER ($p<0.001$) compared with placebo ($p<0.05$). The most common adverse events associated with quetiapine XR were dry mouth, somnolence, and sedation. Greater weight gain was observed in patients on quetiapine XR relative to placebo.

Irritability Associated with Autism

aripiprazole (Abilify)

In an 8-week double-blind, randomized, placebo-controlled, parallel-group study the short-term efficacy and safety of aripiprazole in the treatment of irritability in children and adolescents with autistic disorder was studied in 218 children and adolescents (aged 6 to 17 years).[399] Patients received aripiprazole (5, 10, or 15 mg/day) or placebo. At week 8, all aripiprazole doses produced significantly greater improvement than placebo in mean Aberrant Behavior Checklist Irritability subscale scores (5 mg/day, -12.4; 10 mg/day, -13.2; 15 mg/day, -14.4; versus placebo, -8.4; all $p<0.05$). All aripiprazole doses demonstrated significantly greater improvements in mean CGI-I score than placebo at week 8. Discontinuation rates due to adverse events were as follows: placebo 7.7%, aripiprazole 5 mg/day 9.4%, 10 mg/day 13.6%, and 15 mg/day 7.4%. The most common adverse event leading to discontinuation was sedation. There were 2 serious adverse events: presyncope (5 mg/day) and aggression (10 mg/day). Mean weight change (last observation carried forward) at week 8, was:

placebo +0.3 kg, aripiprazole 5 mg/day +1.3 kg, 10 mg/day +1.3 kg, and 15 mg/day +1.5 kg; all p<0.05 versus placebo.

risperidone (Risperdal)

The efficacy of risperidone in the treatment of irritability associated with autistic disorder was established in 2 8-week, placebo-controlled trials in children and adolescents (aged 5 to 16 years) who met the DSM-IV criteria for autistic disorder.[400] In Study 1 (n=101), patients received twice daily doses of placebo or risperidone, starting at 0.25 mg/day or 0.5 mg/day depending on baseline weight (< 20 kg and ≥ 20 kg, respectively) and titrated to clinical response (mean modal dose of 1.9 mg/day, equivalent to 0.06 mg/kg/day). Risperidone significantly improved scores on the Aberrent Behavior Checklist (ABC-I) and on the CGI-C scale compared with placebo. The ABC-I subscale is an irritability subscale rated by the parent or primary caretaker. In Study 2 (n=55), patients received placebo or risperidone 0.02 to 0.06 mg/kg/day given once or twice daily, starting at 0.01 mg/kg/day and titrated to clinical response (mean modal dose of 0.05 mg/kg/day, equivalent to 1.4 mg/day). Risperidone significantly improved scores on the ABC-I subscale compared with placebo.

Major Depressive Disorder

aripiprazole (Abilify)

A multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of oral aripiprazole as adjunctive therapy in the treatment of major depressive disorder (MDD).[401] Patients were screened for 7 to 28 days to determine if they met DSM-IV criteria for MDD. Patients meeting the study criteria were assigned to receive 8 weeks of single-blind placebo as an adjunct treatment to the standard antidepressant therapy. Antidepressant therapy comprised of 1 of the following: escitalopram, fluoxetine, paroxetine CR, sertraline, or venlafaxine ER. After the 8 weeks of antidepressant monotherapy, patients who had an incomplete response were then randomized to receive either adjunctive placebo (n=178) or adjunctive aripiprazole (n=184; 2 to 15 mg/day when taking fluoxetine or paroxetine; 2 to 20 mg/day with all other antidepressants). The primary endpoint was to determine the mean change from the end of the 8 week prospective treatment to the end of the double-blind treatment utilizing the MADRS total score as the quantifier. Baseline MADRS scores were similar between groups (mean MADRS total score of 26), and the mean change in MADRS total score was significantly greater in the adjunctive aripiprazole treatment group (-8.8) compared to the adjunctive placebo group (-5.8; p<0.001). Adverse events most commonly reported in placebo versus aripiprazole were akathisia (4.5% versus 23.1%, respectively), headache (10.8% versus 6%, respectively), and restlessness (3.4% versus 14.3%, respectively). Discontinuation of treatment due to adverse events was low with only 1.7% of patients receiving placebo and 2.2% of patients receiving aripiprazole.

A second multicenter, randomized, double-blind, placebo-controlled study with 381 patients evaluated the efficacy and safety of oral aripiprazole as adjunctive therapy in MDD.[402] Patients were screened for 7 to 28 days, and then the patients meeting DSM-IV criteria were prospectively assigned to receive antidepressant in addition to adjunct single-blind placebo. Antidepressants were escitalopram, fluoxetine, paroxetine CR, sertraline, or venlafaxine ER and were assigned based on the clinician's preference. After 8 weeks of prospective treatment, incomplete responders were randomized to receive either adjunctive placebo (n=190) or adjunctive aripiprazole (n=191) for 6 weeks. Starting dose of the adjunctive aripiprazole was 5 mg/day with dose adjustments ranging between 2 mg/day to

20 mg/day; the mean endpoint dose was 11 mg/day. The primary efficacy endpoint was based on the mean change in MADRS total score from the end of the prospective treatment phase to the end of the randomized treatment phase. Results demonstrated that adjunctive aripiprazole had a significantly greater change in the mean MADRS total score versus adjunctive placebo during the randomized treatment phase (-8.5 versus -5.7, p=0.001). In addition, adjunctive aripiprazole had significantly greater remission rates than adjunctive placebo (25.4% versus 15.2%, p=0.016), and significantly greater response rates (32.4% versus 17.4%, p<0.001). Adverse events occurring in ≥10% of patients treated with either adjunctive aripiprazole or placebo included akathisia (25.9% versus 4.2%, respectively), headache (9% versus 10.5%, respectively), and fatigue (10.1% versus 3.7%, respectively). Incidence of discontinuation of treatment due to adverse events was low for both adjunctive aripiprazole and adjunctive placebo (3.7% versus 1.1%, respectively).

A multicenter, double-blind, placebo-controlled efficacy trial examined the efficacy of lower doses of aripiprazole (2 mg and 5 mg) as adjunctive treatment of current antidepressant therapy for patients diagnosed with major depressive disorder (MDD).[403] Initially, 221 patients were recruited to participate in the 60 day double-blind augmentation comparison study. The study was divided in 2 phases, each 30 days in length. The parallel comparison design randomized patients to receive aripiprazole 2 mg (phase 1) then aripiprazole 5 mg (phase 2), placebo for both phases, or placebo (phase 1) then aripiprazole 2 mg (phase 2). The current dose of the antidepressant was maintained throughout this 60-day trial. This analysis only reported results from the 39 patients who were randomized to aripiprazole (phase 1) and then increased to 5 mg (phase 2) using the last observation carried forward (LOCF) technique to handle missing data. The primary endpoint measured for treatment success included change in MADRS score, and included secondary outcome measures of QIDS-SR, CGI-S, CGI-I, and PHQ-9. The findings suggest that low dose aripiprazole may have modest advantage over placebo in target outcome response rates, but the results did not reach statistical significance (phase 1 p ≥0.05; phase 2 p=0.5). These modest improvements are in contrast with other clinical studies that have identified a higher response rate with lithium augmentation and alternative non-antipsychotic augmentation strategies (e.g., bupropion and buspirone).

brexpiprazole (Rexulti) and placebo

Two 6-week, double-blind, placebo-controlled, fixed-dose trials in adult patients were performed to evaluate the efficacy of brexpiprazole in the adjunctive treatment of MDD. [404] Study participants were required to meet the DSM-IV-TR criteria for MDD, with or without anxiety symptoms, have an inadequate response to prior antidepressant therapy (1 to 3 courses) in the current episode, and show an inadequate response (symptoms persisted without substantial improvement) throughout the 8 weeks of prospective antidepressant treatment (escitalopram, fluoxetine, paroxetine controlled-release, sertraline, duloxetine delayed release, or venlafaxine extended-release). Patients in Study 1 were randomized to brexpiprazole 2 mg once daily or placebo. Patients in Study 2 were randomized to brexpiprazole 1 mg or 3 mg once daily or placebo. All patients assigned to brexpiprazole started therapy with 0.5 mg once daily during week 1 then, at week 2, the dosage was increased to 1 mg daily in all treatment groups. Starting at week 3, patients were either maintained on 1 mg or increased to 2 mg or 3 mg once daily and maintained for the remaining 4 weeks. The primary endpoint was a change in MADRS score from baseline to week 6. In Studies 1 and 2, brexpiprazole [+ antidepressant (ADT)] 2 mg daily and 3 mg daily were superior when compared to placebo + ADT in difference in mean MADRS total scores (-3.2 [95% CI, -4.9 to -1.5] and -2 [95% CI, -3.4 to -0.5], respectively).

olanzapine / fluoxetine combination (Symbyax), olanzapine (Zyprexa), and fluoxetine

Two parallel, 8-week, double-blind studies compared olanzapine/fluoxetine combination, oral olanzapine, and fluoxetine in outpatients with treatment-resistant depression, defined as a documented history of current-episode antidepressant failure plus a prospective failure of fluoxetine.[405] Following an 8-week fluoxetine lead-in, 605 non-responders with DSM-IV MDD were randomly assigned to olanzapine/fluoxetine combination, olanzapine, or fluoxetine. The primary outcome measure was baseline-to-endpoint mean change on the MADRS. Patients having failed treatment with 2 antidepressants taking olanzapine/fluoxetine combination exhibited greater improvement in depressive symptoms than patients taking olanzapine or fluoxetine in 1 of 2 studies and in the pooled analysis.

quetiapine XR (Seroquel XR) and placebo

Data were analyzed from 2 6-week, multicenter, double-blind, randomized, placebo-controlled studies, prospectively designed to be pooled. Patients received once-daily quetiapine XR 150 mg daily (n=309), 300 mg daily (n=307) or placebo (n=303) adjunctive to ongoing antidepressant therapy.[406] Quetiapine XR (150 mg and 300 mg daily) reduced MADRS total scores compared to placebo at every assessment including week 6 (-14.5, -14.8, -12 for 150 mg, 300 mg, and placebo, respectively; $p<0.001$ each dose) and week 1 (-7.8, -7.3, -5.1 for 150 mg, 300 mg, and placebo, respectively; $p<0.001$ each dose). For quetiapine XR 150 mg and 300 mg daily and placebo at week 6, MADRS response (defined as ≥ 50% decrease in total score) was 53.7% ($p=0.063$), 58.3% ($p<0.01$), and 46.2%, respectively, and MADRS remission (defined as total score ≤ 8) was 35.6% ($p<0.01$), 36.5% ($p<0.001$), and 24.1%, respectively. Quetiapine XR 150 mg and 300 mg daily significantly improved HAM-D, HAM-A, PSQI, and CGI-S scores at week 6 compared to placebo.

META-ANALYSES

A meta-analysis of the efficacy and safety of second generation antipsychotics (SGAs) in the treatment of acute mania was conducted based on randomized, controlled trials comparing SGAs with placebo, first generation antipsychotics, or mood stabilizers found in the PsiTri and MEDLINE databases.[407] Data on efficacy, global dropout, dropout due to adverse events, dropout due to inefficacy, weight gain, rate of somnolence, and EPS were extracted and combined in meta-analysis. A total of 24 studies with 6,187 patients were included. The SGAs were more efficacious than placebo. The addition of antipsychotic agents to mood stabilizer treatment was more effective than treatment with mood stabilizers alone. The SGAs demonstrated efficacy comparable with that of mood stabilizers. Some SGAs seemed to induce more extrapyramidal symptoms than placebo. The SGAs were associated with higher rates of somnolence than placebo.

A meta-analysis to systematically review the effectiveness of co-therapy compared with monotherapy for patients with bipolar mania was conducted using data on mania outcomes, withdrawals, extrapyramidal symptoms, and weight gain extracted from randomized controlled trials retrieved from MEDLINE, Embase, Psychinfo, the Cochrane Library, and reference lists.[408] Each trial was assessed for susceptibility to bias. Pooled effect estimates were summarized as relative risks (RR) or differences in mean values (MD), where appropriate. Eight eligible studies were included with 1,124 participants. Significant reductions in mania based on the Young Mania Rating Scale (YMRS) were shown for haloperidol, oral olanzapine, oral risperidone, and quetiapine as co-therapy compared with monotherapy with a mood stabilizer. For SGAs combined, the pooled difference in mean scores was

4.41 (95% confidence interval [CI], 2.74 to 6.07). Significantly more participants on co-therapy met the response criterion (≥50% reduction in YMRS score). With some drugs, co-therapy decreased tolerability compared with monotherapy and resulted in greater weight gain. There were not sufficient data to compare 1 co-therapy regimen with another. The meta-analysis concluded that addition of antipsychotic treatment to established mood stabilizer treatment is more effective than treatment with mood stabilizer alone.

A 2003 Cochrane review reported that oral olanzapine, lithium, and valproate are relatively equal in terms of effectiveness for the treatment of acute mania; however, lithium and valproate may take days to weeks for the patient to experience a full therapeutic response.[409] Acutely manic patients may require an antipsychotic drug or temporary treatment with a benzodiazepine.

SUMMARY

There is inconclusive evidence that the overall effectiveness of second generation antipsychotics is better than that for first generation agents in terms of meeting primary outcomes of changes in rating scale scores, particularly considering the length of these studies, which is rarely beyond 12 weeks. Second generation antipsychotics are associated with less EPS than first generation antipsychotics; however, the presence of EPS is a treatable condition. The question of long-term adverse events with second generation antipsychotic use remains unresolved. Second generation antipsychotics have largely replaced first generation antipsychotics in the treatment of psychotic disorders, but the long-term effectiveness and adverse event profiles of these products have not been shown to be definitively better.

Currently, inconclusive data exist concerning which second generation antipsychotic agent to use first, but various guidelines exist to help guide the clinician in choosing the best individualized treatment for schizophrenia, bipolar disorder, or major depressive disorder. Relative occurrences of adverse events can be used to guide product selection: weight gain, glucose abnormalities, lipid abnormalities, and diabetes occur more frequently with clozapine (Clozaril, Fazaclo, Versacloz) and olanzapine (Zyprexa, Zyprexa Relprevv). Clozapine has also been associated with orthostatic hypotension leading to rare collapse and respiratory/cardiac arrest and rare fatal myocarditis. Risperidone (Risperdal, Risperdal Consta) and paliperidone (Invega, Invega Sustenna, Invega Trinza) have been associated with prolactin elevation more frequently than other second generation antipsychotics. Lurasidone (Latuda) is contraindicated when used concomitantly with strong CYP 3A4 inducers/inhibitors. Asenapine (Saphris), clozapine (Clozaril, Fazaclo, Versacloz), iloperidone (Fanapt), paliperidone ER (Invega, Invega Sustenna, Invega Trinza), and ziprasidone (Geodon) have a warning of QT prolongation and risk of sudden death due to cardiac conduction abnormalities. Paliperidone ER has a warning against its use in patients with gastrointestinal strictures due to reports of obstructions. Aripiprazole (Abilify), brexpiprazole (Rexulti), quetiapine (Seroquel, Seroquel XR), and olanzapine/fluoxetine (Symbyax) have a boxed warning concerning an increased risk of suicidality in children, adolescents, and young adults with major depressive disorders. All antipsychotics have a boxed warning regarding an increased incidence of mortality when these agents are used in elderly patients with dementia-related psychosis.

The only inhaled antipsychotic available, loxapine inhalation powder (Adasuve), is approved for acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. It carries clinical restrictions including a boxed warning regarding bronchospasm that can potentially lead to respiratory distress or arrest.

Clozapine is used for patients with treatment-resistant schizophrenia and in patients with recurrent suicidal behavior at high risk of suicide. Clozapine is reserved for refractory patients due to rare reports of agranulocytosis and seizures occurring, among other serious adverse events, and patients taking it must have regular white blood cell and absolute neutrophil counts closely monitored.

There are not enough comparative data to support distinctions among the injectable second generation antipsychotics. Injectable risperidone is the only intramuscular product approved for maintenance therapy of bipolar disorder.

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